

EXHIBIT A

United States Patent [19]**Barrie et al.**[11] **Patent Number:** **5,604,213**[45] **Date of Patent:** **Feb. 18, 1997**[54] **17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT**[75] Inventors: **Susan E. Barrie, Kent; Michael Jarman, London; Gerard A. Potter, Cheshire; Ian R. Hardcastle, Sutton,** all of Great Britain[73] Assignee: **British Technology Group Limited,** London, England[21] Appl. No.: **315,882**[22] Filed: **Sep. 30, 1994****Related U.S. Application Data**

[63] Continuation-in-part of PCT/GB93/00531 May. 15, 1993.

[30] **Foreign Application Priority Data**

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Jul. 14, 1994	[GB]	United Kingdom	9414192

[51] **Int. Cl.⁶** **A61K 31/58; C07J 43/00**[52] **U.S. Cl.** **514/176; 540/95**[58] **Field of Search** **540/95; 514/176**[56] **References Cited****FOREIGN PATENT DOCUMENTS**

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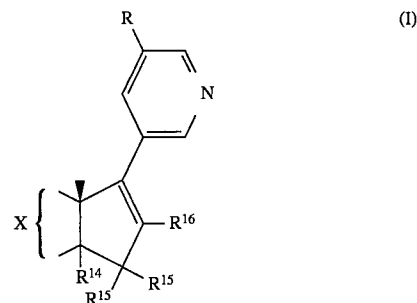
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(List continued on next page.)

Primary Examiner—Mukund J. Shah**Assistant Examiner**—Anthony Bottino**Attorney, Agent, or Firm**—Nixon & Vanderhye[57] **ABSTRACT**

Compounds of the general formula (1)



wherein X represents the residue of the A, B and C rings of a steroid, R represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, R¹⁴ represents a hydrogen atom and R¹⁵ represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, or a hydroxy or alkylcarbonyloxy group of 2 to 5 carbon atoms or R¹⁴ and R¹⁵ together represent a double bond, and R¹⁶ represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, are useful for treatment of androgen-dependent disorders, especially prostatic cancer, and also oestrogen-dependent disorders such as breast cancer.

22 Claims, No Drawings

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17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT

This specification is a continuation-in-part of PCT Application PCT/GB93/00531, filed Mar. 15, 1993 and which designated the United States of America.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to 17-substituted steroids and their use in the treatment of androgen-dependent and oestrogen-dependent disorders, especially prostatic cancer and breast cancer respectively.

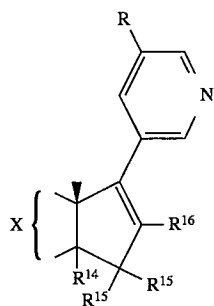
2. Description of the Related Art

The 17 α -hydroxylase/C₁₇₋₂₀ lyase enzyme complex (hereinafter "hydroxylase/lyase") is known to be essential for the biosynthesis of androgens and oestrogens. In the treatment of androgen-dependent disorders, especially prostatic cancer, there is a need for strong inhibitors of hydroxylase/lyase. Certain anti-androgenic steroids are well known, for example Cyproterone acetate (17 α -acetoxy-6-chloro-1 α , 2 α -methylene-4,6-pregnadiene-3,20-dione). Many other steroids have been tested as hydroxylase/lyase inhibitors. See, for example, PCT Specification WO 92/00992 (Schering AG) which describes anti-androgenic steroids having a pyrazole or triazole ring fused to the A ring at the 2,3-position, or European Specifications EP-A 288053 and EP-A 413270 (Merrell Dow) which propose 17 β -cyclopropylamino androst-5-en-3 β -ol or -4-en-3-one and their derivatives.

SUMMARY OF THE INVENTION

It has now surprisingly been found that steroids lacking a C₂₀ side chain and having a 17-(3-pyridyl) ring in its place, together with a 16,17-double bond, are powerful hydroxylase/lyase inhibitors, useful for the above-stated purposes.

According to the invention, there are provided compounds of the general formula



wherein X represents the residue of the A, B and C rings of steroid, R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms, R¹⁴ represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R¹⁵ substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R¹⁴ and one of the R¹⁵ groups together represent a double bond and the other R¹⁵ group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R¹⁶ represents a hydrogen atom, halogen atom, or an alkyl group of 1 to

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4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts.

The term "steroid" herein includes any compound having the steroidal B and C rings, but in which all or part of the A ring is missing e.g. ring not closed (lacking the 2- or 3-position C-atom or both) or takes the form of a cyclopentane ring. It also includes azasteroids having a ring nitrogen atom in place of a ring carbon atom, especially in the A-ring such as in 4-azasteroids.

In general, the compounds of formula (1) are new and such compounds per se are included in the invention. However, certain of them have been disclosed as intermediates in the synthesis of certain steroids having a 3-pyridyl or 3-pyridonyl group in the 17 β -position, see J. Wicha and M. Masnyk, Bulletin of the Polish Academy of Sciences: Chemistry 33 (1-2), 19-27 and 29-37 (1985). The first of these papers says that a 17 β -side chain of the form —C=C—C=O or —C=C—C=N favours cardiotonic properties and describes the synthesis of 17 β -(3-pyridyl)-14 β -androst-4-ene-3 β ,14-diol, while the second uses this compound to prepare 17 β -[3-pyrid-2(1H)onyl]-14 β -androst-4-ene-3 β ,14-diol. Those final compounds differ from those of the present invention by having a saturated D-ring and the paper contains no test results. Insofar as certain compounds within formula (1) are known as intermediates in these syntheses, the invention extends to the compounds only for use in therapy. These are 3 β -acetoxy-17-(3-pyridyl)androst-5,14,16-triene and 3 β ,15 α - and 3 β ,15 β -diacetoxy-17-(3-pyridyl)androst-5,16-diene. See also J. Wicha et. al., Heterocycles 20, 231-234 (1983) which is a preliminary communication of the first of the above two papers.

J. Wicha et. al., Bulletin of the Polish Academy of Sciences, Chemistry 32 (1-2), 75-83 (1984) have also described the preparation of 3 β -methoxy-17 β -(3-pyridyl)androstane and pyridone analogues thereof via the intermediate 3 β -methoxy-17-(3-pyridyl)-5 α -androst-16-ene. Accordingly, the invention extends to the latter compound only for use in therapy. A preliminary communication of this paper, by J. Wicha and M. Masnyk, appeared in Heterocycles 16, 521-524 (1981).

The invention also includes pharmaceutical compositions comprising a compound of formula (1) in association with a pharmaceutically acceptable diluent or carrier. The terminology "pharmaceutical compositions" implies that injectible formulations are sterile and pyrogen-free and thereby excludes any compositions comprising the compound of formula (1) and a non-sterile organic solvent, such as may be encountered in the context of the final stages of preparing these above-mentioned compounds of formula (1) which have been described in the literature but without any therapeutic use being mentioned.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the compounds of the invention the essential structural features comprise all of:

- a 3-pyridyl ring in the 17-position
- a ring double bond in the 16,17-position of the D-ring
- the 18-position methyl group

It is critical that the pyridine nitrogen atom be in the 3-position, not the 2- or 4-position. It is also critical that the pyridine ring be joined directly to the 17-carbon atom. This criticality is demonstrated by tests of inhibiting activity against hydroxylase and lyase (Table 1). The concentration of test compound required to achieve 50% inhibition of the

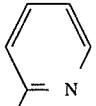
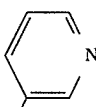
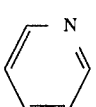
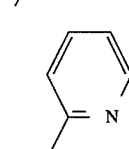
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enzyme is far greater for the 2-pyridyl, 4-pyridyl and 2-pyridylmethyl compounds tested than for the 3-pyridyl. The methods of determination were as described in the Examples hereinafter.

TABLE 1

Effect of variations in the 17-substituent on inhibition of hydroxylase and lyase, demonstrating the criticality of the 17-substituent in this invention.

R ¹⁷	Type	IC ₅₀ (μM)	
		Lyase	Hydroxylase
	2-Pyridyl (for comparison)	0.13	0.32
	3-pyridyl (present invention)	0.003	0.004
	4-pyridyl (for comparison)	2.0	5.0
	2-picoyl (for comparison)	>10	>10

Note:

all the compounds of formula (2) tested were poor inhibitors of aromatase: IC₅₀ >20 μM.

Our modelling of the geometry of the putative transition state of the lyase component of the hydroxylase-lyase enzyme complex, in the putative mechanism of action of the lyase component, suggests that the 16,17-double bond is essential to allow the 3-pyridine ring to adopt the orientation required for co-ordination to the haem group of the hydroxylase-lyase complex.

Elsewhere, the D-ring can have any other simple substituent. Certain simple substituents are defined in connection with the preferred general formula (1), but it will be appreciated that others could be substituted for those of formula (1). In the compounds of formula (1), R¹⁵ is preferably hydrogen or alkyl of 1 to 3 carbon atoms, R¹⁶ hydrogen, alkyl of 1 to 3 carbon atoms, fluorine, chlorine, bromine or iodine, and R hydrogen or methyl, in the 5-position of the pyridine ring.

The remainder of the molecule, designated "X" in formula (1), can be of any kind conventional in steroid chemistry or have any other feature known in steroids having anti-androgenic activity, for example the pyrazole or triazole ring, fused to the A ring at the 2- and 3- positions, disclosed

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in the above-cited Specification WO 92/00992, or oxazole ring fused in the same positions.

By way of example, X can represent the residue of

androstan-3α- or 3β-ol,
androst-5-en-3α- or 3β-ol,
androst-4-en-3-one,
androst-2-ene,
androst-4-ene,
androst-5-ene,
androsta-5,7-dien-3α or 3β-ol,
androsta-1,4-dien-3-one,
androsta-3,5-diene,
estra-1,3,5[10]-triene,
estra-1,3,5[10]-trien-3-ol,
5α-androstan-3-one,
androst-4-ene-3,11-dione,
6-fluoroandrost-4-ene-3-one or
androstan-4-ene-3,6-dione

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters, especially 3-alkanoates and -benzoates, to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-7,8-, 9,11- and 11,12-positions

as 3-oximes

as 3-methylenes

as 3-carboxylates

as 3-nitriles

as 3-nitros

as 3-desoxy derivatives

to have one or more hydroxy, halo, C₁₋₄-alkyl, trifluoromethyl, C₁₋₄-alkoxy, C₁₋₄-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B or C-ring

to be 19-nor.

Preferred C₁₋₄-alkyl and alkoxy groups are methyl and ethoxy.

Preferred C₁₋₄-alkanoyloxy groups are acetoxo and propanoyloxy.

Preferred halo groups are fluoro, bromo and chloro and the preferred substitution position is the 6-position.

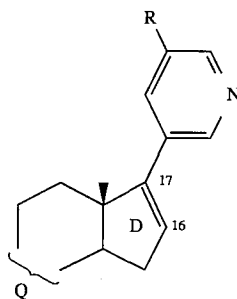
The substituents include, for instance, 2-fluoro, 4-fluoro, 6-fluoro, 9-fluoro, 3-trifluoromethyl, 6-methyl, 7-methyl, 6-oxo, 7-oxo, 11-oxo, 6-methylene, 11-methylene, 4-hydroxy, 7-hydroxy, 11-hydroxy or 12-hydroxy, each in any appropriate epimeric form, and, subject to structural compatibility (well known in general steroid chemistry), in any combination of two or more such groups.

Compounds which are likely to be unstable are considered excluded from consideration. Such compounds will be evident to steroid chemists. Compounds having esoteric substituents likely to interfere with the stereochemical alignment of the steroid molecule with the enzymes to be inhibited, by virtue of steric or electronic distribution effects, are to be avoided. For example, a 2,3,5,6-tetrafluoro-4-trifluoromethylphenoxy substituent in the 3-position is not recommended. Androst-5-en-3β-ol having such an ether substituent in place of the 3β-hydroxy group has been shown to be a very poor inhibitor for lyase and hydroxylase.

The currently preferred compounds of formula (1) include those which are saturated and unsubstituted at the 11- and 12-positions and which therefore are of the general formula (3):

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wherein Q represents the residue of A, B and C rings of steroid, and R is a hydrogen atom or an alkyl group of 1-4 carbon atoms.

However, 11- and/or 12-substituted compounds are also active. Particularly preferred are 11-oxo and 11 β -hydroxy derivatives of compounds of formula (3).

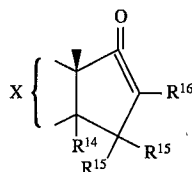
Specifically preferred compounds of the invention comprise

17-(3-pyridyl)androsta-5,16-dien-3 β -ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5 α -androst-16-en-3 α -ol
and their acid addition salts and 3-esters.

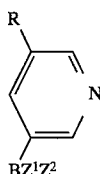
Other notable compounds of the invention comprise
17-(3-pyridyl)-5 α -androst-16-en-3-one,
17-(3-pyridyl)-androsta-4,16-diene-3,11-dione,
17-(3-pyridyl)-androsta-3,5,16-trien-3-ol,
6 α - and 6 β -fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one
17-(3-pyridyl)androsta-4,16-dien-3,6-dione,
17-[3-(5-methyl pyridyl)]androsta-5,16 dien-3 β -ol
3 α -trifluoromethyl-17-(3-pyridyl)androsta-16-en-3 β -ol
and their acid addition salts and 3-esters.

Insofar as certain compounds within formula (1) are known per se and these are compounds which are less easy to prepare than many of the others, a preferred class of compounds of formula (1) is those which do not have a 3 β -alkoxy group, a 14,15-double bond or a 15-ester group.

The compounds of formula (1) can be prepared by a method which is in itself novel and inventive. Starting from a 17-oxo compound of general formula (4):



wherein X, R¹⁴, R¹⁵ and R¹⁶ are as defined above and any other oxo groups and hydroxy groups in the molecule are first appropriately protected, the method comprises replacing the 17-hydroxy group of compound (4) in its enol form by a leaving group (L) which is capable of being replaced by a 3-pyridyl group in a palladium complex-catalysed cross-coupling reaction with a pyridyl ring-substituted boron compound of formula (5):



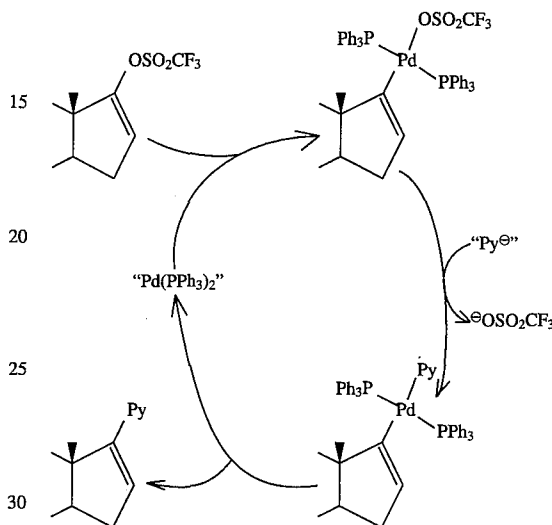
wherein Z¹ and Z² independently represent hydroxy or alkoxy or alkyl of 1-4 carbon atoms each, preferably 1-3

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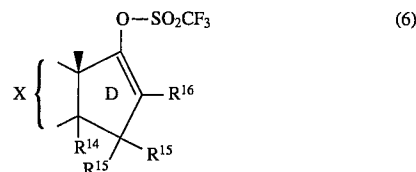
carbon atoms, most preferably ethyl or methoxy, or Z¹ and Z² together represent an alkylendioxy group of 2 or 3 carbon atoms and R is as defined above and carrying out said cross-coupling reaction.

The palladium complex-catalysed cross-coupling reaction of the 17-substituted steroid with the boron compound is believed to involve the steps indicated in the following illustrative reaction scheme 1 (Py=3-pyridyl). The pyridyl anionic species is provided by the boron compound.

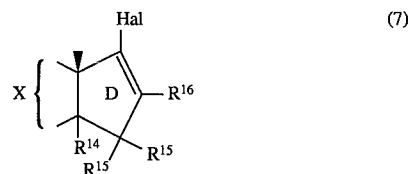
Scheme 1



The replacement of the 17-enol group can be, for example, to form a 16,17-ene trifluoromethanesulphonate ("triflate") of formula (6):



or a 17-iodo or bromo-16,[17]-ene (a "vinyl halide") of formula (7):



(Hal=I or Br)

Compounds of formula (6) can be prepared by reacting the 17-oxo compound of formula (4) with an enol ester-forming trifluoromethanesulphonic acid derivative such as the anhydride, see S. Cacchi, E. Morera and G. Ortar, Tetrahedron Letters, 25, 4821 (1984). The 17-oxo compound can be considered notionally to exist in the enol form, the reaction being one of esterification of the enol.

For the preparation of the 17-position derivatives of formula (6) or (7) any necessary protection of other groups in the molecule may be first carried out. For example in the triflate route hydroxyl groups are conveniently protected as their acetates, whilst in the vinyl halide route the 3-oxo group of steroids can be selectively protected as their perfluorotolyl enol ethers, see M. Jarman and R. McCague, J.Chem. Soc. Perkin Trans. 1, 1129 (1987).

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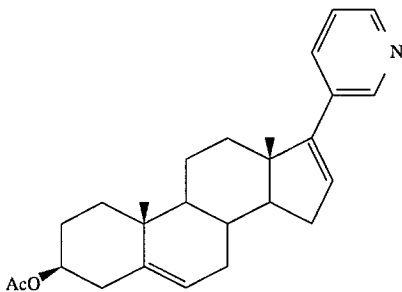
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Compounds of formula (7) can be prepared by first hydrazinating the 17-oxo compounds of formula (4) by a standard method to form the 17-hydrazone, which is then reacted with bromine or iodine in the presence of an amine or guanidine base, see D. Barton, G. Bashiardes and J. Fourmy, Tetrahedron Letters, 24, 1605 (1983).

The 17-position derivative (whether triflate or vinyl halide) is then reacted with the boron compound of formula (5) using as catalyst a palladium(0) phosphine complex, for example tetrakis(triphenylphosphine)palladium(0), or a palladium (II) phosphine complex which is reducible in situ to a palladium(0) phosphine species, especially bis(triphenylphosphine)palladium (II) chloride.

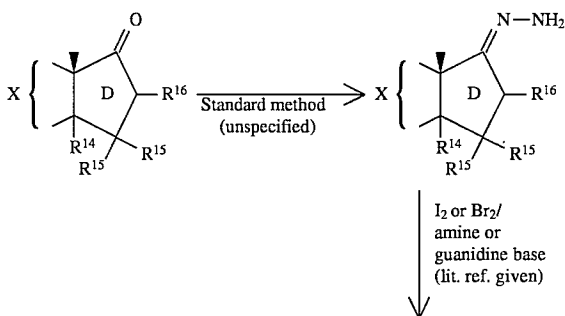
SUMMARY OF THE INVENTION

The vinyl halide route, via a compound of formula (7), is particularly well suited to the preparation of 3 β -acyloxy-16, 17-ene-17-(3-pyridyl) steroids, especially the preferred compound, 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene, of formula (8):



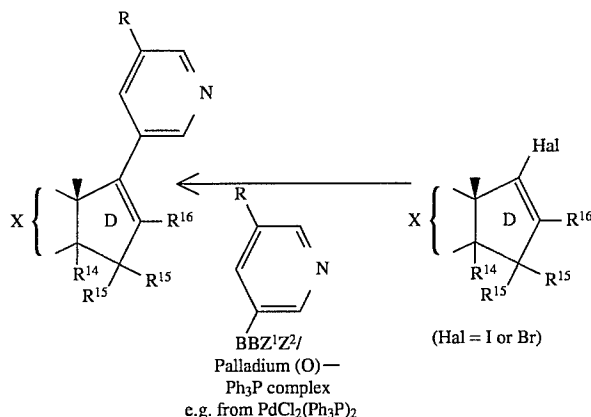
but using the unprotected 3 β -hydroxy compound as starting material. By-products can be reduced either (a) by keeping the proportion of organoboron compound (borane) used in the cross-coupling reaction within the range 1.0 to 1.2 equivalents per equivalent of steroid or (b) by crystallising the reaction product of the cross-coupling reaction from a mixture of acetonitrile and methanol. This route via the vinyl iodide intermediate is therefore amenable to large scale synthesis, and is shown in Scheme 2 below.

Scheme 2



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-continued
Scheme 2



The principle of this aspect of the invention may be expressed as a method of preparing a 3 β -hydroxy- or 3 β -(lower acyloxy)-16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3 β -(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3 β -hydroxy-16,17-ene-17-iodo or-bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane, in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, especially with a said borane of formula (5), wherein R is a hydrogen atom or an alkyl group of 1-4 carbon atoms and Z¹ and Z² independently represent hydroxy or alkoxy or alkyl or 1-3 carbon atoms each or Z¹ and Z² together represent an alkylenedioxy group of 2 or 3 carbon atoms, in a proportion of at least 1.0 equivalent of boron compound per equivalent of steroid, in an organic liquid, which is a solvent for the 3 β -hydroxy steroidal reaction product, and optionally esterifying the 3 β -hydroxy reaction product to the 3 β -acyloxy ester, which method comprises feature (a) or (b) above.

Preferably the vinyl iodide or bromide is unsubstituted in the 14, 15 and 16-positions, in which case it can be prepared from dehydroepiandrosterone (DHEA). In the hydrazination it is preferable to use hydrazine hydrate together with a catalytic amount of a proton provider which is most preferably hydrazine sulfate.

The hydrazone is preferably iodinated with iodine or brominated with bromine in the presence of a strong base such as a tetraalkylguanidine, especially tetramethylguanidine which is cheaply and readily available.

In the cross-coupling reaction, the boron compound is preferably a diethylborane or a dimethoxyborane (Z¹=Z²=Et or OMe). Other boranes include those in which the boron atom is part of a cyclic ether ring e.g. as in Z¹, Z²=1,2-ethylenedioxy or 1,3-propylenedioxy. In embodiment (a) of this aspect of the invention the proportion of borane added is at least 1.0, but no more than 1.2 equivalents of boron per equivalent of steroid, preferably about 1.1, but in the embodiment (b) a higher proportion is preferred, e.g. from 1.2:1 to 1.5:1 equivalents of boron compound to steroid. The higher proportion will give the better yield of product but also more of the contaminating boron, phosphine and/or palladium compounds. According to embodiment (b), however, these are removed with the acetonitrile solvent. In either embodiment, the palladium compound is a palladium (0) phosphine complex such as tetrakis(triphenylphosphine)palladium (0) or a compound reducible to a palladium (0)

phosphine species, especially bis(triphenylphosphine) palladium (II) chloride. The reaction vessel is preferably purged with an inert gas, especially argon or nitrogen, to minimise the possibility of oxidation with a corresponding redox reduction of palladium to the metallic state.

The cross-coupling reaction is preferably carried out in two phases, one aqueous, one organic. The organic phase comprises an organic solvent for the 3 β -hydroxy steroidal reaction product, especially tetrahydrofuran (THF). Other cyclic ethers such as dioxane could be used in place of THF. Preferably, a nucleophilic activator, such as sodium carbonate, is used, in which case it is normally present in the aqueous phase.

After the reaction, inorganic salts can be removed by first adding another organic solvent, preferably diethyl ether, which is a solvent for the organoboron contaminants produced in the reaction product, and miscible with the first-mentioned organic solvent (e.g. THF), but immiscible with water, whereafter the organic, e.g. THF-diethyl ether, phase and water (aqueous phase) can be separated. After this separation, various work-up procedures are operable. In one procedure, particularly suited to embodiment (a), the THF and diethyl ether are removed, e.g. evaporated as a mixture, and the remaining reaction product is washed with a third organic solvent, which can be diethyl ether, preferably cooled to below room temperature, most especially to 10° C. or lower. The third organic solvent is one in which the 3 β -hydroxy steroid reaction product has a low solubility and which, importantly, removes the organoboron compound/s (and also the contaminating phosphine and palladium compound/s). Diethyl ether is preferred.

A different work-up procedure, used in embodiment (b), comprises crystallisation from acetonitrile/methanol. Acetonitrile is a preferred crystallisation solvent to keep boron compound as well as palladium compound in solution and is therefore used in an excess over methanol e.g. an excess of at least 5:1 and preferably about 8:1 by volume.

To prepare the 3 β -acyloxy (alkylcarbonyloxy) compounds, of which the acetoxy compound is preferred, standard acylating (acyl-esterification) agents such as acetyl, propionyl or butyryl chloride or anhydride can be used. The final esterification product may be crystallised direct from hexane, rather than from ethanol/water followed by hexane. Preferably, the work-up procedure comprises reverse phase chromatography, i.e. using a relatively lipophilic solid phase. In this procedure, the chief by-product, a bis-steroidal compound, is preferentially retained on the solid phase and can be eluted with a good separation from the desired product.

Further compounds of the invention can be prepared by standard steroid to steroid inter-conversion chemistry, so long as the D-ring chemical structure is not affected thereby. If the D-ring structure is likely to be affected, it would usually be necessary to prepare the desired compound de novo, i.e. by choosing the appropriate starting compound of formula (4), protected if necessary, and carrying out the reactions of 17-substitution of the enol and cross-coupling with the boron compound as described above.

By way of example, the 3-esters of steroid 3-ol with an alkanolic acid of 1 to 6 carbon atoms, or a cycloalkanoic acid or aralkanoic acid such as phenylacetic or phenylpropionic acid, an aroic acid such as benzoic acid, or other simple organic acid such as methanesulphonic acid, can be converted into the 3-ol or the 3-ol to the 3-ester. Other examples of simple conversions which would not affect the D-ring structure are

- i) Oppenauer oxidation using cyclohexanone and aluminium isopropoxide to convert 3-hydroxy to 3-oxo steroids and notably $\Delta^{5,6}$ -3-hydroxy to $\Delta^{4,5}$ -3-oxo steroids;

- ii) Wittig olefination to convert oxo groups to methylene groups [D. D. Evans et al., J. Chem. Soc., 4312-4317, (1963)];

- iii) Oxidation of Δ^5 -3 β -hydroxy to Δ^4 -3,6-dione steroids using N-methylmorpholine N-oxide and tetra-n-propylammonium perruthenate catalyst [M. Moreno et al., Tetrahedron Letters, 32, 3201-3204, (1991)];

- iv) 6-Methylenation of Δ^4 -3-oxo steroids using formaldehyde dimethylacetal [K. Annen et al., Synthesis, 34-40 (1982)];

- v) Conversion of Δ^4 -3-oxo to 4,4-dimethyl- Δ^5 -3-oxo, $\Delta^{1,4}$ -3-oxo, $\Delta^{1,4,6}$ -3-oxo, 7 α -methyl- Δ^4 -3-oxo, $\Delta^{4,6}$ -3-oxo, 6-chloro- $\Delta^{4,6}$ -3-oxo, $\Delta^{2,4}$ -2,3-isoxazole, 6 α -methyl- Δ^4 -3-oxo and Δ^4 -3-desoxy; Δ^5 -3 β -ol to 5 α -fluoro-6-oxo, 5 α ,6,6-trifluoro, 6,6-difluoro and 6 α -fluoro- Δ^4 -3-oxo; and 11-oxo to 11-hydroxy and $\Delta^{9,11}$ steroids [D. Lednicher and L. A. Mitscher, The Organic Chemistry of Drug Synthesis, Is. 2 and 3, Wiley (1980 and 1984)] or

- vi) Electrophilic fluorination of steroids using N-fluoropyridinium reagents [T. Umenoto et al., Organic Synthesis 69, 129-143 (1990)].

The compounds of formula (1) may be prepared as salts, e.g. the hydrochloride and converted to the free base form and thereafter to such other conventional pharmaceutically acceptable salts as acetates, citrates and lactates, as may seem appropriate.

The present invention also provides a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the invention, in association with a therapeutically acceptable carrier or diluent. The composition of the invention can, for example, be in a form suitable for parenteral (e.g. intravenous, intramuscular or intracavitary), oral, topical or rectal administration. Particular forms of the composition may be, for example, solutions, suspensions, emulsions, creams, tablets, capsules, liposomes or micro-reservoirs, especially compositions in orally ingestible or sterile injectable form. The preferred form of composition contemplated is the dry solid form, which includes capsules, granules, tablets, pills, boluses and powders. The solid carrier may comprise one or more excipients, e.g. lactose, fillers, disintegrating agents, binders, e.g. cellulose, carboxymethylcellulose or starch or anti-stick agents, e.g. magnesium stearate, to prevent tablets from adhering to tableting equipment. Tablets, pills and boluses may be formed so as to disintegrate rapidly or to provide slow release of the active ingredient.

The present invention also includes a method of treating androgen- and oestrogen-dependent disorders, especially tumours, and most especially pro static tumours, in the mammalian body, which comprises administering a compound of the invention to a mammalian patient in a therapeutically effective dose, e.g. in the range 0.001-0.04 mmole/kg body weight, preferably 0.001-0.01 mmole/kg, administered daily or twice daily during the course of treatment. This works out (for humans) at 20-800 mg/patient per day. The preferred use is in treating prostatic cancer. Another use is in treating breast cancer.

The following Examples illustrate the invention.

EXAMPLE 1

- (a) 3 β -Acetoxyandrost-5,16-dien-17-yl trifluoromethanesulphonate

To a stirred solution of dehydroepiandrosterone-3-acetate (24.8 g, 75 mmol) in dry dichloromethane (500 ml) containing 2,6-di-*t*-butyl-4-methylpyridine (18.5 g, 90 mmol) was added trifluoromethanesulphonic anhydride (12.6 ml,

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75 mmol). After 12 h the mixture was filtered and washed with water (50 ml), dried (MgSO_4), and the solvent evaporated. Chromatography, on elution with light petroleum-dichloromethane (6:1), gave firstly androsta-3,5,16-trien-17-yl trifluoromethanesulphonate (3.02 g, 10%) as an oil. $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 0.99 (3H,s,18- CH_3), 1.02 (3H,s,19- CH_3), 5.39 (1H,m,6-H), 5.59 (1H,m,16-H), 5.62 (1H,m,3-H), 5.93 (1H,dm,J 9.4 Hz,4-H); MS m/z 402 (M^+). Further elution with light petroleum-dichloromethane (3:1) afforded the title compound (20.1 g, 58%) which crystallised from hexane, m.p. $75^\circ\text{--}76^\circ\text{C}$. $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.00 (3H,s, 18- CH_3), 1.06 (3H, s,19- CH_3), 2.04 (3H,s,C H_3CO_2), 4.59 (1H,m,3 α -H), 5.39 (1H,dm,J 4.9 Hz,6-H), 5.58 (1H,m,16-H). Anal. Calcd: C,57.13; H,6.32; S,6.93. Found: C,57.29; H,6.31; S,6.96%.

(b) 3 β -Acetoxy-17-(3-pyridyl)androsta-5,16-diene

Diethyl(3-pyridyl)borane (3.38 g, 23 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 3 β -acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate (6.94 g, 15 mmol) in THF (75 ml) containing bis(triphenylphosphine)palladium(II) chloride (0.105 g, 0.15 mmol). An aqueous solution of sodium carbonate (2M, 30 ml) was then added and the mixture heated, with stirring, by an oil bath at 80°C for 1 h, and allowed to cool. The mixture was partitioned between diethyl ether and water, the ether phase was dried (Na_2CO_3), filtered through a short plug of silica, and concentrated. Chromatography, on elution with light petroleum-diethyl ether (2:1), afforded the title compound (4.95 g, 84%) which crystallised from hexane, m.p. $144^\circ\text{--}145^\circ\text{C}$. $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.05 (3H,s, 19- CH_3), 1.08 (3H,s,18- CH_3), 2.04 (3H,s, CH_3CO_2), 4.60 (1H,m,3 α -H), 5.42 (1H,dm, J 4.7 Hz,6-H), 5.99 (1H,m,16-H), 7.23 (1H,m,Py 5-H) 7.65 (1H,m,Py 4-H), 8.46 (1H,m,Py 6-H), 8.62 (1H,m,Py 2-H). Anal. Calcd: C, 79.75; H, 8.50; N, 3.58. Found: C, 79.78; H, 8.52; N, 3.54%.

EXAMPLE 2

17-(3-Pyridyl)androsta-5,16-dien-3 β -ol

To a solution of 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene (4.90 g, 12.5 mmol) in methanol (50 ml) was added an aqueous solution of sodium hydroxide (10% w/v, 10 ml) and the mixture heated, with stirring, on an oil bath at 80°C for 5 min., then allowed to cool. The mixture was poured into water, neutralised with hydrochloric acid (1M), rebaseified with saturated sodium bicarbonate solution, and extracted with hot toluene (3×100 ml). The toluene extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with toluene-diethyl ether (2:1) afforded the title compound (3.45 g, 79%) which crystallised from toluene, mp $228^\circ\text{--}229^\circ\text{C}$; $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.05 (3H,s,19- CH_3), 1.07 (3H,s,18- CH_3), 3.54 (1H,m,3 α -H), (5.40H,dm,J 5.0 Hz, 6-H), 5.99 (1H,m,16-H), 7.22 (1H,m,Py5-H), 7.65 (1H,m,Py 4-H), 8.46 (1H,m,Py 6-H), 8.62 (1H,m,Py 2-H). Anal. Calcd: C, 82.47; H, 8.94; N, 4.01. Found: C, 82.40; H, 8.91; N, 3.97%.

EXAMPLE 3

17-(3-Pyridyl)androsta-3,5,16-triene

The method followed that described in Example 1, using in step (b) diethyl(3-pyridyl)borane (0.88 g, 6.0 mmol), androsta-3,5,16-trien-17-yl trifluoromethanesulphonate (2.01 g, 5.0 mmol), prepared in step (a), THF (25 ml), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol), and aqueous sodium carbonate (2M, 10 ml). Chromatography, on elution with dichloromethane, afforded the title compound (1.39 g, 84%) which crystallised from hex-

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ane, m.p. $110^\circ\text{--}112^\circ\text{C}$. $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.02 (3H,s,19- CH_3), 1.07 (3H,s,18- CH_3), 5.44 (1H,m,6-H), 5.61 (1H,m,3-H), 5.95 (1H,dm, J 9.8 Hz, 4-H), 6.01 (1H,m,16-H), 7.23 (1H,m,Py 5-H), 7.66 (1H,m,Py 4-H), 8.46 (1H,m,Py 6-H), 8.63 (1H,m,Py 2-H); MS m/z 331 (M^+).

EXAMPLE 4

(a) 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]androsta-3,5,16-trien-17-yl trifluoromethanesulphonate

The method followed that described in Example 1(a) but using 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]androsta-3,5-dien-17-one (5.03 g, 10 mmol), prepared as described in M. Jarman and R. McCague, J. Chem. Soc., Perkin Trans. 1, 1129 (1987), dichloromethane (80 ml), 2,6-di-*t*-butyl-4-methylpyridine (2.87 g, 14 mmol), and trifluoromethanesulphonic anhydride (1.85 ml, 11 mmol). Chromatography, on elution with light petroleum-dichloromethane (10:1), afforded the title compound (1.93 g, 30%) which crystallised from ethanol, m.p. $106^\circ\text{--}107^\circ\text{C}$. $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.02 (6H,s,18 and 19- CH_3), 5.16 (1H,s,4-H), 5.28 (1H,m,6-H), 5.59 (1H,m,16-H); MS m/z 634 (M^+).

(b) 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]-17-(3-pyridyl)androsta-3,5,16-triene

The method essentially followed that of Example 1(b) but using diethyl(3-pyridyl)borane (0.44 g, 3.0 mmol), 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]androsta-3,5,16-trien-17-yl trifluoromethanesulphonate (1.27 g, 2.0 mmol), THF (10 ml), bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.1 mmol), and aqueous sodium carbonate (2M, 5 ml). Chromatography, on elution with light petroleum-diethyl ether (3:1), afforded the title compound (0.82 g, 73%) which crystallised from hexane, m.p. $166.0^\circ\text{--}166.5^\circ\text{C}$. $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.05 (3H,s,19- CH_3), 1.07 (3H,s,18- CH_3), 5.18 (1H,s,4-H), 5.32 (1H,m,6-H), 6.01 (1H,m,16-H), 7.23 (1H,m,Py 5-H), 7.66 (1H,m,Py 4-H), 8.47 (1H,m,Py 6-H), 8.63 (1H,m,Py 2-H). Anal. Calcd: C, 66.07; H, 5.01; N, 2.49; F, 23.60. Found: C, 65.97; H, 5.02; N, 2.47; F, 23.41%.

(c) 17-(3-Pyridyl)androsta-4,16-dien-3-one

To solution of 3-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]-17-(3-pyridyl)androsta-3,5,16-triene (0.423 g, 0.75 mmol) in THF (5 ml) was added ethanol (5 ml) followed by aqueous hydrochloric acid (1M, 5 ml) and the mixture heated, with stirring, by an oil bath at 65°C for 48h and allowed to cool. The mixture was poured into water (20 ml), neutralised with aqueous sodium hydroxide (1M), and extracted with diethyl ether (3×30 ml). The ether extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with diethyl ether, afforded the title compound (185 mg, 71%) which crystallised from diethyl ether, m.p. $148^\circ\text{--}150^\circ\text{C}$. IR ν_{max} 1674 cm^{-1} ; $^1\text{H-NMR}(\text{CDCl}_3)$ inter alia δ 1.07 (3H,s,18- CH_3), 1.24 (3H,s,19- CH_3), 5.76 (1H,s,4-H), 5.99 (1H,m,16-H), 7.23 (1H,m,Py 5-H), 7.64 (1H,m,Py 4-H), 8.47 (1H,m,Py 6-H), 8.62 (1H,m,Py 2-H); MS m/z 347 (M^+).

EXAMPLE 5

(a) 3-Acetoxyestra-1,3,5[10],16-tetraen-17-yl trifluoromethanesulphonate

The method followed that described in Example 1(a), but using oestrone-3-acetate (4.69 g, 15 mmol), dichloromethane (120 ml), 2,6-di-*t*-butyl-4-methylpyridine (4.00 g, 19.5 mmol), and trifluoromethanesulphonic anhydride (2.8 ml, 16.5 mmol). Chromatography, on elution with light petroleum-dichloromethane (3:1), afforded the title com-

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pound (5.21 g, 78%). ¹H-NMR(CDCl₃) inter alia δ1.00(3H, s, 18-CH₃), 2.29(3H, s, CH₃CO₂), 5.62(1H, m, 16-H), 6.81(1H, m, ArH), 6.85(1H, m, ArH), 7.26(1H, m, ArH). Anal. Calcd. for C₂₁H₂₃O₅F₃S₁·½H₂O: C, 55.62; H, 5.34. Found: C, 55.58; H, 5.14%.

(b) 3-Acetoxy-17-(3-pyridyl)estra-1,3,5[10],16-tetraene

The method followed that described in Example 1(b), but using diethyl(3-pyridyl)borane (1.65 g, 11.2 mmol), 3-acetoxyestra-1,3,5[10],16-tetraen-17-yl trifluoromethanesulphonate (3.56 g, 8.0 mmol), THF (40 ml), bis(triphenylphosphine)palladium(II) chloride (56 mg, 0.08 mmol), and aqueous sodium carbonate (2M, 15 ml).

Chromatography, on elution with light petroleum-diethyl ether (2:1) afforded the title compound (2.40 g, 80%). ¹H-NMR(CDCl₃) inter alia δ1.04(3H, s, 18-CH₃), 2.29(3H, s, CH₃CO₂), 6.03(1H, m, 16-H), 6.82(1H, m, ArH), 6.85(1H, m, ArH), 7.24(1H, m, Py 5-H), 7.29(1H, m, ArH), 7.69(1H, m, Py 4-H), 8.48(1H, m, Py 6-H), 8.65(1H, m, Py 2-H); MS m/z 373. (M⁺).

EXAMPLE 6

17-(3-Pyridyl)estra-1,3,5[10],16-tetraen-3-ol

The method followed that described in Example 2, but using 3-acetoxy-17-(3-pyridyl)estra-1,3,5[10],16-tetraene (2.36 g, 6.3 mmol), methanol (40 ml), aqueous sodium hydroxide (10% w/v, 5 ml), and the mixture was heated at 80° C. for 10 min. Chromatography, on elution with toluene-methanol (8:1), afforded the title compound (1.40 g, 67%) which crystallised from toluene, m.p. 256°–258° C.: ¹H-NMR(DMSO) inter alia δ1.01(3H, s, 18-CH₃), 6.15(1H, m, 16-H), 6.47(1H, m, ArH), 6.52(1H, m, ArH), 7.04(1H, m, ArH), 7.35(1H, m, Py 5-H), 7.79(1H, m, Py 4-H), 8.45(1H, m, Py 6-H), 8.62(1H, m, Py 2-H). Anal. Calcd: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.39; H, 7.78; N, 4.06%.

EXAMPLE 7

3α-Acetoxy-17-(3-pyridyl)-5α-androst-16-ene

The method followed that described in Example 1, using in step (b) diethyl(3-pyridyl)borane (1.41 g, 9.6 mmol), 3α-acetoxy-5α-androst-16-en-17-yl trifluoromethanesulphonate (3.44 g, 7.4 mmol), prepared from the 3α-acetoxy-5α-androstan-17-one by the method of step (a), THF (40 ml), bis(triphenylphosphine)palladium(II) chloride (52 mg, 0.07 mmol), and aqueous sodium carbonate (2M, 15 mmol). Chromatography, on elution with light petroleum-diethyl ether (2:1), afforded the title compound (2.39 g, 82%), ¹H-NMR(CDCl₃) inter alia δ0.85(3H, s, 19-CH₃), 1.01(3H, s, 18-CH₃), 2.06(3H, s, CH₃CO₂), 5.02(1H, m, 3β-H), 6.00(1H, m, 16-H), 7.24(1H, m, Py 5-H), 7.68(1H, m, Py 4-H), 8.47(1H, m, Py 6-H), 8.63(1H, m, Py 2-H); MS m/z 393 (M⁺).

EXAMPLE 8

17-(3-Pyridyl)-5α-androst-16-en-3α-ol

The method followed that described in Example 2, but using 3α-acetoxy-17-(3-pyridyl)-5α-androst-16-ene (2.33 g, 5.9 mmol), methanol (40 ml), aqueous sodium hydroxide (10% w/v, 8 ml), and the mixture was heated at 80° C. for 20 min. Chromatography, on elution with toluene-methanol (40:1), afforded the title compound (1.62 g, 78%) which crystallised from toluene, m.p. 198°–199° C.: ¹H-NMR(CDCl₃) inter alia δ0.84(3H, s, 19-CH₃), 1.00(3H, s, 18-CH₃), 4.06(1H, m, 3β-H), 5.97(1H, m, 16-H), 7.21(1H, m, Py 5-H), 7.64(1H, m, Py 4-H), 8.45(1H, m, Py 6-H), 8.61(1H, m, Py

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2-H). Anal. Calcd: C, 82.00; H, 9.46; N, 3.99. Found: C, 81.78; H, 9.47; N, 3.96%.

EXAMPLE 9

17-(3-Pyridyl)-5α-androst-16-en-3-one

From a solution of 17-(3-Pyridyl)-5α-androst-16-en-3α-ol (1.05 g, 3.0 mmol) in dry toluene (60 ml) and cyclohexanone (10 ml) was distilled off part of the solvent (20 ml) to eliminate moisture. After allowing to cool to 90° C., aluminium isopropoxide (1.02 g, 5.0 mmol) was added and the mixture heated under reflux for 90 min. then allowed to cool. The mixture was diluted with diethyl ether (250 ml), washed with aqueous trisodium citrate (15% w/v; 2×30 ml), dried (Na₂CO₃), and concentrated. Chromatography, on elution with toluene-methanol (40:1), afforded the title compound (0.90 g, 86%) which crystallised from toluene, m.p. 190°–192° C. IR ν_{max} 1713 cm⁻¹; ¹H-NMR(CDCl₃) inter alia δ1.04(3H, s, 19-CH₃), 1.07(3H, s, 18-CH₃), 5.98(1H, m, 16-H), 7.22(1H, m, Py 5-H), 7.64(1H, m, Py 4-H), 8.46(1H, m, Py 6-H), 8.61(1H, m, Py 2-H); MS m/z 349 (M⁺). Anal. Calcd: C, 82.47; H, 8.94; N, 4.01. Found: C, 82.00; H, 8.94; N, 3.84%.

EXAMPLE 10

a) 3-(tert-Butyldimethylsiloxy)androsta-3,5-diene-11,17-dione

To a solution of adrenosterone (6.0 g, 20 mmol) in dry dichloromethane (120 ml) was added triethylamine (8.4 ml, 60 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (5.0 ml, 22 mmol) and the mixture stirred at room temperature for 3 h. The dichloromethane was evaporated and the residue redissolved in diethyl ether (100 ml), then allowed to stand for 30 min, after which time an oil separated. The ether phase was decanted off the oil and the solvent evaporated to give the title compound which was used directly in step (b). IR ν_{max} 1705, 1747 cm⁻¹; ¹H-NMR(CDCl₃) inter alia δ0.12(6H, s, Me₂Si), 0.85(3H, s, 18-CH₃), 0.92(9H, s, BuSi), 1.17(3H, s, 19-CH₃), 4.73(1H, dm, J 6.9 Hz, 6-H), 5.36(1H, m, 4-H).

b) 13-(tert-Butyldimethylsiloxy)-11-oxo-androsta-3,5,16-trien-17-yl trifluoromethanesulfonate

To a solution of the product from step (a) in dry THF (100 ml), cooled to -78° C., was added a freshly prepared solution of lithium diisopropylamide [prepared by adding n-butyllithium (1.6M; 13.8 ml, 22 mmol) in hexane to a solution of diisopropylamine (3.1 ml, 22 mmol) in dry THF (25 ml) at -18° C.] and the resultant yellow solution stirred at -78° C. for 30 min. A solution of N-phenyltrifluoromethanesulfonimide (7.15 g, 20 mmol) in dry THF (20 ml) was then added and after an additional 1 h. at -78° C. was allowed to reach ambient temperature. The reaction mixture was poured into water (200 ml) and extracted with diethyl ether (2×200 ml), the combined ether extracts were washed with water (20 ml), dried Na₂CO₃, and concentrated to give the title compound which was used directly in step (c). IR ν_{max} 1710 cm⁻¹; ¹H-NMR(CDCl₃) inter alia δ0.13(6H, s, Me₂Si), 0.92(9H, s, Bu Si), 1.35(6H, 2s, 18-CH₃ and 19-CH₃), 4.75(1H, m, 6-H), 5.38(1H, s, 4-H), 5.68(1H, m, 16-H). c) 3-(tert-Butyldimethylsiloxy)-17-(3-pyridyl)androsta-3,5,16-trien-11-one

The method essentially followed that described in Example 1(b), but using the 13-(tert-butyldimethylsiloxy)-11-oxo-androsta-3,5,16-trien-17-yltrifluoromethanesulfonate from step (b), diethyl(3-pyridyl)borane (3.53 g, 24 mmol), THF (100 ml), bis(triphenylphosphine)palladium(II) chloride (280 mg, 0.4 mmol), and aqueous sodium carbonate (2M; 50 ml). Following work-up as described in

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Example 1(b) the title compound was obtained, which was used directly in step (d). IR ν_{max} 1705 cm^{-1} , $^1\text{H-NMR}$ (CDCl_3) inter alia δ 0.13 (3H,s,Me₂Si), 0.93 (9H,s,^tBuSi), 0.99 (3H,s,18-CH₃), 1.18 (3H,s,19-CH₃), 4.75 (1H,m,6-H) 5.37 (1H,m,4-H), 6.09 (1H,m,16-H), 7.26 (1H,m,Py 5-H), 7.62 (1H,m,Py 4-H), 8.50 (1H,m,Py 6-H), 8.60 (1H,m,Py 2-H). MS m/z 475 (M⁺).

d) 17-(3-Pyridyl)androsta-4,16-diene-3,11-dione

To a solution of the product from step (c) in wet THF (60 ml) was added a solution of tetrabutylammonium fluoride (1.0M; 10 ml, 10 mmol) in THF, and the mixture stirred at room temperature for 12 h. The mixture was partitioned between diethyl ether and water basified with saturated aqueous sodium bicarbonate, the ether phase isolated, dried (Na_2CO_3), and concentrated. Chromatography, on elution with diethyl ether, afforded the title compound (4.30 g, 60% overall yield from adrenosterone) which crystallised from diethyl ether, m.p. 181°–183° C.

IR ν_{max} 1669, 1703 cm^{-1} , $^1\text{H-NMR}$ (CDCl_3) inter alia δ 1.02 (3H,s,18-CH₃), 1.45 (3H,s,19-CH₃), 5.76 (1H,s,Py 4-H), 6.08 (1H,m,16-H) 7.24 (1H,m,Py 5-H), 7.59 (1H,m,Py 4-H), 8.50 (1H,m,Py 6-H), 8.59 (1H,m,Py 2-H). MS m/z 361 (M⁺). Anal Calcd: C, 79.74; H,7.53; N,3.88. Found: C,79.58; H,7.57; N,3.89%.

EXAMPLE 11

3-Acetoxy-17-(3-pyridyl)androsta-3,5,16-triene

17-(3-pyridyl)androsta-4,16-dien-3-one (174 mg, 0.50 mmol) was dissolved in isopropenyl acetate (2 ml). p-Toluenesulfonic acid (130 mg, 0.68 mmol) was then added and the mixture heated at 80° C. for 12 h. After allowing to cool the mixture was poured into diethyl ether, washed with saturated aqueous sodium bicarbonate, dried (Na_2CO_3) and concentrated. Chromatography on elution with light petroleum-diethyl ether (1:1), afforded the title Compound (86 mg, 44%), IR ν_{max} 1755 cm^{-1} , $^1\text{H-NMR}$ (CDCl_3) inter alia δ 1.05 (6H,s,18-CH₃ and 19-CH₃), 2.15 (3H,s,COCH₃) 5.44 (1H,m,6-H), 5.72(1H,m,4-H), 6.00 (1H,m,16-H), 7.25 (1H,m,Py 5-H), 7.66 (1H,m,Py 4-H), 8.47 (1H,m,Py 6-H), 8.63 (1H,m,Py 2-H). MS m/z 389 (M⁺).

EXAMPLE 12

6 β -Fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one and

EXAMPLE 13

6 α -Fluoro-17-(3-pyridyl)androsta-4,16-dien-13-one

To a solution of 3-acetoxy-17-(3-pyridyl)androsta-3,5,16-triene (80 mg, 0.21 mmol) in dry dichloromethane (2 ml) was added N-fluoropyridinium trifluoromethanesulfonate (180 mg, 0.73 mmol) and the mixture heated under reflux for 12 h. The mixture was diluted with diethyl ether (30 ml), washed with dilute aqueous sodium hydroxide (0.5M; 2 \times 5 ml), dried Na_2CO_3 , and concentrated. ^1H and $^{19}\text{F-NMR}$ at this stage showed the 6-fluorinated products were formed as a 3:2 mixture of the β and α -epimers. Chromatography, on elution with light petroleum-diethyl ether (1:2), gave firstly:-i) the title 6 β -epimer (13 mg, 17%) as white crystals, m.p. 167°–169° C. IR ν_{max} 1684 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) inter alia δ 1.11 (3H,s,18-CH₃), 1.37 (3H,s,19-CH₃), 5.06 (1H,dd, $J_{\text{H-H}}$ 2.4 Hz, $J_{\text{H-F}}$ 49 Hz, 6 α -H), 5.92 (1H,m,4-H), 6.01 (1H,m,16-H), 7.24 (1H,m,Py 5-H), 7.65 (1H,m,Py 4-H), 8.48 (1H,m,Py 6-H), 8.63 (1H,m,Py 2-H). $^{19}\text{F-NMR}$ δ -165.9 (dt, $J_{\text{H-F}}$ 49 Hz, 6 β -F). MS m/z 365 (M⁺).

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Further elution afforded:

ii) The title 6 α -epimer (8 mg, 11%) as white crystals, m.p. 167°–169° C., IR ν_{max} 1681 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) inter alia δ 1.07 (3H,s,18-CH₃), 1.24 (3H,s,19-CH₃), 5.18 (1H, dm, $J_{\text{H-F}}$ 48 Hz, 6 β -H), 5.98 (ZH,m,4-H and 16-H), 7.26 (1H,m,Py 5-H), 7.64 (1H,m,Py 4-H), 8.40 (1H, m,Py6-H), 8.63 (1H,m,Py 2-H). $^{19}\text{F-NMR}$ (CDCl_3) δ -183.9 (d, $J_{\text{H-F}}$ 48 Hz, 6 α -F). MS m/z 365 (M⁺).

EXAMPLE 14

17-(3-pyridyl)androsta-4,16-dien-3-one (via Oppenauer Oxidation)

This Example illustrates a better method of preparing the compound already prepared in Example 4. The method followed that described in Example 9, but using 17-(3-pyridyl)androsta-5,16-dien-3 β -ol (1.05 g, 3.0 mmol). Chromatography, on elution with toluene-methanol (20:1), afforded the title compound (0.85 g, 82%), which crystallised from diethyl ether, m.p. 148°–150° C. Spectroscopic data was identical to that given in Example 4(c). Anal. Calcd: C,82.95; H,8.41; N,4.03 Found: C,83.00; H, 8.50; N,3.99%

EXAMPLE 15

17-(3-pyridyl)androsta-4,16-dien-3-one oxime

To a suspension of 17-(3-pyridyl)androsta-4,16-dien-3-one (125 mg, 0.36 mmol) in ethanol (2 ml) was added hydroxylamine hydrochloride (50 mg, 0.72 mmol), followed by pyridine (0.2 ml), and the mixture heated under reflux for 1 h. then allowed to cool. The solvent was evaporated and the crystalline product triturated under water, collected on a sinter, washed with cold water, and dried in vacuo to give the title oxime as a 1:1 mixture of syn and anti geometric isomers. $^1\text{H-NMR}$ (CDCl_3) inter alia δ 1.06 (3H,s,18-CH₃), 1.13 (3H,s,19-CH₃), 5.75 and 5.80 (1H,2m, isomeric 4-H), 6.01 (1H,m,16-H), 7.26 (1H,m,Py 5H), 7.68 and 7.88 (1H, 2m, isomeric Py 4-H), 8.48 and 8.53 (1H, 2m, isomeric Py 6-H), 8.63 (1H,m,Py 2-H). MS m/z 362 (M⁺).

EXAMPLE 16

17-(3-pyridyl)androsta-4,16-diene-3,6-dione

To a solution of 17-(3-pyridyl)androsta-5,16-dien-3 β -ol (350 mg, 1.0 mmol) in dry dichloromethane (10 ml) was added N-methylmorphine N-oxide (351 mg, 3.0 mmol) followed by 400 mg of freshly dried and powdered 4 Å molecular sieves and the mixture stirred for 10 min. Tetrapropylammonium perruthenate catalyst (35 mg), 0.1 mmol) was then added, the reaction flask placed in an ultrasonic bath, and the mixture irradiated whilst maintaining the temperature between 20°–30° C. for 2 h. The mixture was then filtered, diluted with diethyl ether, washed with water, dried (Na_2CO_3), and concentrated. Chromatography, on elution with diethyl ether-ether acetate (5:1), afforded the title compound (26 mg, 7%) as white crystals m.p. 210°–212° C. IR ν_{max} 1680 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) inter alia δ 1.10 (3H,s,18-CH₃), 1.44 (3H,s,19-CH₃), 4.42 (1H,m, enolic 2-H), 5.84 (1H,s,4-H), 6.01 (1H,m,16-H), 7.24 (1H, m,Py 5-H), 7.65 (1H,m,Py 4-H), 8.45 (1H,m,Py 4-H), 8.45 (1H,m,Py 6-H), 8.60 (1H,m,Py 2-H). FAB-MS m/z 362 (M+1).

EXAMPLE 17

3 α -(Trifluoromethyl)-17-(3-pyridyl)androsta-16-en-3 β -ol

To a solution of 17-(3-pyridyl)androsta-16-en-3-one (100 mg, 0.29 mmol) in THF (2 ml) cooled to 0° C. was added trifluoromethyltrimethylsilane (200 μ l, 1.3 mmol) followed

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by tetrabutylammonium fluoride trihydrate (10 mg, 0.03 mmol). After 30 min., dilute aqueous hydrochloric acid (1M; 1 ml) was added and the mixture stirred at room temperature for 12 h. The mixture was then basified with saturated aqueous sodium bicarbonate and extracted with diethyl ether. The three extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with light petroleum-diethyl ether (1:1), afforded the title compound (87 mg, 73%) which crystallised from toluene, m.p. 192°–193° C. $^1\text{H-NMR}$ (CDCl_3) δ 0.92 (3H,s,19- CH_3), 1.01 (3H,s,18- CH_3), 5.98 (1H,m,16-H), 7.22 (1H,m,Py 5-H), 7.64 (1H,m,Py 4-H), 8.45 (1H,m,Py 6-H), 8.60 (1H,m,Py 2-H); $^{19}\text{F-NMR}$ (CDCl_3) δ -79.1 (s,3 α - CF_3). MS m/z 419 (M+). Anal. Calcd: C,71.57; H,7.69; N,3.34; F,13.59 Found: C,71.67; H,7.71; N,3.25; F,13.30%.

EXAMPLE 18

(a) Diethyl[3-(5-methylpyridyl)]borane

3-Bromo-5-methylpyridine, which can be prepared as described in the literature, e.g. L. van der Does and H. J. van Hertog, *Rec. Trav. Chem. Pays Bas* 84, 957–960 (1985) or R. A. Abramovitch and M. Saha, *Can. J. Chem.* 44, 1765–1771 (1966), is reacted with *n*-butyllithium, according to the method of M. Terashima et al., *Chem. Pharm. Bull.* 31, 4573–4577, (1983). The product is treated with triethylborane and then iodine.

(b) 17-[3-(5-Methylpyridyl)]androsta-5,16-dien-3 β -ol

Diethyl [3-(5-methylpyridyl)]borane is reacted with 3 β -acetoxyandrosta-5,16-dien-17-yl trifluoromethane sulphonate analogously to Example 1(b) and the resulting 3 β -acetate is hydrolysed with sodium hydroxide, analogously to Example 2, to yield the title compound.

The following Examples illustrate preparation of compounds of the invention by the vinyl halide route. In Example 19, the 3 β -hydroxy product is produced without chromatography, by embodiment (a). In Example 20, the 3 β -hydroxy product is not isolated, but in step (d) an impurity has been identified as a 16,17-bis(steroidal) by-product. This can be removed by reverse phase chromatography, but now that the by-product has been identified, those skilled in the art will be able more easily to identify procedures which will remove it, without the need for chromatography. Further, it is believed that with the higher organoboron:steroid ratios suggested above, the side-reaction leading to this impurity will be reduced.

EXAMPLE 19

(a) Dehydroepiandrosterone-17-hydrazone

To a stirred solution of dehydroepiandrosterone (28.8 g, 0.1 mol) in ethanol (500 ml) was added hydrazine hydrate (19.5 ml, 0.4 mol), followed by a solution of hydrazine sulfate (65 mg, 0.5 mmol) in water (2 ml). After stirring for 3 days the mixture was poured into water (3 liters) to precipitate the product as a white crystalline solid. The product was collected by filtration on a sinter, washed with cold water (2x50 ml), then with Et_2O (50 ml). The product was then dried in vacuo, firstly over silica gel, and finally over P_2O_5 , to give the title compound as a white crystalline solid (29.6 g, 98%).

Notes

1) The method of Schweder et al., p.202, compound No. 2 therein (using triethylamine) gave a very fine crystalline product which was difficult to filter.

2) The method of Schweder et al. p. 203, compound No. 4 therein (using sodium acetate buffer) gave a slightly lower yield (96%) in trial experiments, whereas the modified

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procedure used above gave a product amenable for filtration, and in excellent yield (98%).

(b) 17-Iodo-androsta-5,16-dien-3 β -ol

To a solution of iodine (53.3 g, 0.21 mol) in THF (2 L), cooled by an ice/water bath to 0° C., was added 1,1,3,3-tetramethylguanidine (63 ml, 57.6 g, 0.50 mol).

A solution of dehydroepiandrosterone-17-hydrazone (30.25 g, 0.10 mol) in THF (750 ml) was then added slowly to the above iodine solution via a transfer needle over about 2 h, whilst maintaining the reaction temperature at 0° C. After all the hydrazone solution was added, the mixture was filtered, and the filtrate concentrated. The remaining oil was then heated on an oil bath for 4 h, allowed to cool, and dissolved in Et_2O . The Et_2O solution was washed with 1M HCl until the aqueous phase was acidic, washed with 0.5M NaOH, then 1M $\text{Na}_2\text{S}_2\text{O}_3$, and finally with water. The Et_2O phase was separated, dried (MgSO_4), and concentrated to give the crude product. Recrystallisation from Et_2O /hexane (3:2) afforded the title compound as off-white crystals (35.8 g, 90%).

(c) 17-(3-Pyridyl)androsta-5,16-dien-3 β -ol

Diethyl(3-pyridyl)borane (3.23 g, 22 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 17-iodo-androsta-5,16-dien-3 β -ol (7.96 g, 20 mmol) in THF (120 ml) containing bis(triphenylphosphine)palladium (II) chloride (140 mg, 0.2 mmol). An aqueous solution of sodium carbonate (2M, 50 ml) was then added and the mixture heated, with stirring, by an oil bath at 80° C. for 48 h, and allowed to cool.

The mixture was partitioned between Et_2O and water the organic phase was separated, dried (Na_2CO_3) and twice concentrated from Et_2O by evaporation to remove THF (with Et_2O). The residual solid was then washed with Et_2O (100 ml), the Et_2O solution decanted off, and the remaining white solid recrystallised from toluene (3.94 g, 56%).

Notes

1) The time required for completion needs to be made longer than when using the vinyl triflate (48 h vs 1 h) since it has been found that the vinyl iodide reacts much more slowly.

2) It has been found that a smaller excess of borane than described in the earlier applications (for the vinyl triflate) aids in isolation of product.

3) The work-up procedure enables the product to be isolated without chromatography, thereby enabling scaling up.

(d) 3 β -Acetoxy-17-(3-pyridyl)androsta-5,16-diene

To a stirred suspension of finely powdered 17-(3-pyridyl)androsta-5,16-dien-3 β -ol (3.50 g, 10 mmol) in dry diethyl ether (150 ml) containing triethylamine (2.3 ml, 16 mmol) and dimethylaminopyridine (0.012 g, 0.1 mmol) was added acetyl chloride (1.0 ml, 14 mmol). The mixture was then stirred at ambient temperature for 12 h, over which time a thick white precipitate of triethylammonium chloride had formed. The mixture was then filtered and the filtrate concentrated to afford the crude product which was recrystallised firstly from ethanol/water (1:1), then finally from hexane to afford the title compound (3.30 g, 84%).

EXAMPLE 20

(a) Dehydroepiandrosterone-17-hydrazone

Into a 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed dehydroepiandrosterone (288 g, 1.0 mol) and ethanol (5.0 L). To the resultant stirred solution was added hydrazine hydrate (195 ml, 4.0 mol), followed by a solution of hydrazine sulfate (0.65 g, 0.005 mol) in water

(20 ml) [note: the hydrazine sulfate dissolved in this volume of water at about 40° C.]. After stirring at room temperature for 5 days, water (4.5 L) was added, the mixture poured into water (10 L), and the white crystalline precipitate allowed to settle. The product was collected by filtration on a sinter, washed with cold water (2×500 ml), then with Et₂O (2×500 ml). The product was then dried in vacuo, firstly over silica gel, and finally over P₂O₅, to give the title compound as a white crystalline solid, mp 204°–206° C. (284.8 g, 94%).

(b) 17-Iodo-androsta-5,16dien-3β-ol

A 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was charged with iodine (156.1 g, 0.615 mol), THF (4.0 L; GPR grade), and Et₂O (2.0 L; BDH specially dried grade). The resultant stirred solution was cooled by an ice/water bath to 0° C. and 1,1,3,3-tetramethylguanidine (188 ml, 173 g, 1.50 mol) was added. A solution of dehydroepiandrosterone-17-hydrazone from step (a) (90.74 g, 0.30 mol) in THF (2.25 L) was then added slowly to the above iodine solution via a canula over about 2 h, whilst maintaining the reaction temperature at 0° C. [note: N₂ is evolved as the hydrazone is added to the iodine solution]. After all the hydrazone solution was added, the mixture was stirred for an additional hour and the precipitate allowed to settle [note: a precipitate of tetramethylguanidium iodide forms during the reaction]. The mixture was then filtered, and the filtrate concentrated to an oil on a rotary evaporator.

This reaction was carried out a total of three times, thus using in total 272.22 g (0.90 mol) of dehydroepiandrosterone-17-hydrazone from step (a). The concentrated residues from the three separate reactions were combined and heated on an oil bath for 4 h, then allowed to cool [note: this converts any 17,17-diiodo by-product into the 17-vinyl iodide product]. This oil was then dissolved in Et₂O (5 L), filtered, and further diluted with additional Et₂O (4 L).

The Et₂O solution was washed with aqueous HCl (1M; 3×500 ml) until the aqueous phase was acidic [note: the ether solution changes colour from brown to yellow when the aqueous phase remains acidified] then finally with water (500 ml). The Et₂O phase was separated, dried (MgSO₄), and concentrated to a volume of 3 L, then left to allow the product to crystallise. The yellow crystals were collected by filtration on a sinter, washed with hexane (3×500 ml) and dried under vacuum (335.4 g, 94%). Recrystallisation from ethanol-water (5:1) afforded the product as white crystals (297.3 g, 83%) mp 175°–176° C., lit. mp 173°–174° C. (c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

In a 2 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed the steroidal 17-iodo product from step (b) (98.0 g, 0.246 mol) and this was dissolved in THF (1.1 L). The flask was purged with argon and bis(triphenylphosphine)palladium (II) chloride catalyst (1.73 g, 0.0025 mol) was added, followed by diethyl(3-pyridyl)borane (43.35 g, 0.295 mol). To the resultant orange THF solution was added an aqueous solution of sodium carbonate (2M; 500 ml). The flask was fitted with a reflux condenser, and the apparatus purged again with argon. The mixture was then heated under reflux (at about 80° C.) with stirring on a stirrer/heating mantle (Electrothermal MA) for 4 days [note: upon completion of the reaction the organic phase darkens in colour from orange to dark orange/brown], then allowed to cool. This reaction was carried out a total of three times, thus using a total of 294.0 g (0.74 mol) of the steroidal 17-iodo product from step (b).

The reaction mixtures were combined and Et₂O (5 L) added. The organic phase was separated, washed with water (2 L), and left to give a first crop of crystals which were collected by filtration on a sinter. The filtrate was concen-

trated and the residue redissolved in Et₂O to afford a second crop of crystals. The aqueous phase and washings from the above work-up were extracted with hot toluene (2 L) on a steam bath and concentration of the toluene extracts afforded further product. The combined crude product from the above procedures was then dissolved in the minimum volume of hot methanol, filtered through a plug of "Celite" (Registered Trade Mark) and an equal volume of acetonitrile added to the methanol solution. The acetonitrile/methanol solution was then concentrated to half its original volume on a rotary evaporator and the solution left to crystallise. The resultant white crystals were collected by filtration on a sinter, washed with acetonitrile and dried in vacuo to constant weight (191.1 g, 74%), mp 202°–212° C. A second recrystallisation from toluene-methanol (50:1) afforded the product as white crystals (146.8 g, 57%) mp 214°–218° C., lit. mp 228°–229° C.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

The following reaction was carried out in a 500 ml round-bottomed flask, fitted with a magnetic stirrer bar. To a suspension of the steroidal product from step (c) (26.5 g, 0.104 mol) in dry pyridine (200 ml), was added acetic anhydride (75 ml) and the mixture stirred at room temperature for 24 h. The pyridine and excess acetic anhydride were removed on a rotary evaporator, initially with the water bath at 70° C., and finally at 800° C. for 30 min. The resulting oil was dissolved in Et₂O (500 ml), washed with saturated aqueous NaHCO₃ (2×200 ml), dried (Na₂CO₃), and concentrated to an oil which crystallised on standing. ¹H-NMR spectroscopy at this stage showed the product contained about 5% of a 16,17'-bi(steroidal) contaminant, 3β-acetoxy-16-(3'-β-acetoxyandrosta-5',16'-dien-17'-yl)-17-(3-pyridyl)androsta-5,16-diene, which originated as a by-product from the coupling reaction of step (c).

The product was therefore further purified by preparative flash chromatography using a 9 cm diameter column, with silica stationary phase (Merck 15111), eluting with dichloromethane. The by-product eluted first followed by the desired product, although the separation was incomplete. Fractions containing a significant amount of by-product were combined and subjected to further chromatographic purification.

The foregoing reaction and purification procedure was carried out a total of four times, thus using a total of 146 g (0.418 mol) of the steroidal product from step (c).

The product-containing dichloromethane fractions from the chromatographic purification were concentrated and recrystallised from hexane to afford white crystals which were dried in vacuo to constant weight. The total amount of product obtained was 136.0 g (83%).

The dichloromethane fractions containing the least by-product were combined, and following recrystallisation from hexane, afforded the title compound as white crystals with mp 142°–144° C. Analysis showed this material ("A") contained 6.8% w/w of the bis(steroidal) by-product.

A second crop of white crystals ("B") of the product, containing 21.8% w/w of bis(steroidal) by-product (25 g), was obtained.

The two products were purified using reverse phase chromatography. The column was packed with "LiChro-prep" (Registered Trade Mark) RP-8 reverse-phase C₈ packing, Art. No. 9324, supplied by E. Merck, Darmstadt, Germany. The course of the chromatography was followed by UV detection at 253 nm, with purity checks by HPLC.

Product "A" (10.17 g) was dissolved in 200 ml. hot acetonitrile and 40 ml. hot methanol, and, after being allowed to cool, the filtrate was applied to a 10 cm. diameter

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column containing about 500 g. of the packing. The eluant was 5% 0.05M aqueous ammonium acetate/95% v/v acetonitrile. 7.51 g. of product was recovered in fractions 4–10. Fractions (500 ml) 4–11 contained the product with some impurities, but not the bis-steroidal byproduct. The eluant was changed to 2.5% acetic acid/95.5% v/v acetonitrile and then to 5% acetic acid/95% v/v acetonitrile. A pink colour seen in fractions 16 and 17 evidenced the bis-steroidal by-product. Fraction 18 was colourless. The column can be washed with 100% acetonitrile, for re-use.

Product "B" (1 g) was separated by a similar method except that the product was dissolved initially in 100% acetonitrile and the filtrate applied to a 2 cm. column packed with 100 g. of the solid phase. Excellent separation of the product was achieved with the aqueous ammonium acetate/acetonitrile eluant.

Although, in this Example, the reverse phase column was used in addition to a conventional column, it is clear that the conventional column achieved little separation of the bis-steroidal by-product and it is intended to omit the conventional column in future preparations.

TEST RESULTS

(a) Preparation of testicular material

Human testes were obtained from previously untreated patients undergoing orchidectomy for prostatic cancer. The testes were decapsulated and stored in liquid nitrogen until use. A microsomal preparation was prepared essentially as described by S. E. Barrie et al., J. Steroid Biochem. 6, 1191–5, (1989). The material was then thawed, finely chopped, and homogenised in 0.25M sucrose (5 ml/g wet weight) using a Potter homogeniser. The homogenate was centrifuged at 12000 g for 30 min, and then the microsomes were pelleted by spinning the supernatant at 100,000 g for 1 hr. The pellet was washed by being resuspended in 0.25M sucrose and repelleted. The microsomal pellet was then resuspended in 50 mM sodium phosphate pH 7.4/glycerol (3/1 v/v) and stored in aliquots in liquid nitrogen.

(b) Determination of 17 α -hydroxylase

The basic assay mixture was EDTA (0.2 mM), dithiothreitol (DTT; 0.1 mM), NADPH (0.25 mM), glucose 6-phosphate dehydrogenase (G6PDH; 6.25 μ g/ml), MgCl₂ (1 mM), glucose 6-phosphate (G6P; 10 mM) and the substrate, 3H-progesterone (3 μ M) in sodium phosphate (50 mM), pH 7.4. The compounds under test were dissolved in 50% DMSO and the final concentrations of ethanol and DMSO were 1% each. The assay reaction was carried out for 1 hour and was terminated by the addition of 2 vols. of methanol-acetonitrile (2:1) containing approx. 100 μ M unlabelled progesterone, 17 α -hydroxyprogesterone, androstenedione, testosterone, and 16 α -hydroxyprogesterone. The last-mentioned steroid was added as it appeared that the human enzyme was capable of 16 α -hydroxylation as well as 17 α -hydroxylation.

The separation of the steroids by HPLC was carried out using an "Uptight" guard column packed with 40–63 μ m Nucleosil C18 and a 10 cm main column packed with 5 μ m Nucleosil C18 and 60% methanol as eluant. The radioactivity in the peaks of interest was monitored on-line by mixing the HPLC effluent 1:1 with Ecoscint A (National Diagnostics) scintillation fluid, containing 25% acetonitrile, and passing the mixture through a Berthold LB506C radiochemical monitor. The hydroxylase activity was measured as the production of 17 α -hydroxyprogesterone, androstenedione and testosterone.

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(c) Determination of C₁₇–C₂₀ lyase

The mixture was the same as described above for the 17 α -hydroxylase except that the substrate was ³H-17 α -hydroxy- progesterone. The reaction was carried out for 1–2 h. and was stopped by the addition of 2 vols. of methanol/acetonitrile (2/1 containing approx. 100 μ M 17 α -hydroxyprogesterone, androstenedione and testosterone.

The HPLC separation used for the lyase involved a mini-re-column "Uptight Guard Column" packed with PELL-ODS (pellicular octadecyl silica) and a 10 cm. main column "Apex C18" column packed with 5 μ APEX-CAT silica.

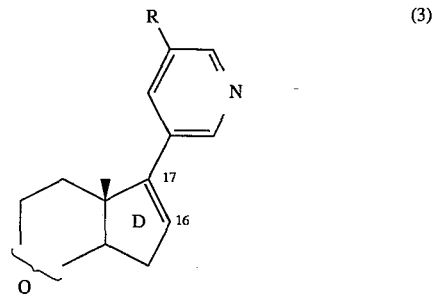
The eluant was 38:12:50 methanol:acetonitrile:water flowing at 1 ml/min. The effluent was mixed 1:1 with Ecoscint A containing 5% methanol and 5% acetonitrile and the radioactivity was measured directly by a Berthold LB506C radiochemical detector. The lyase activity was measured as the production of androstenedione and testosterone.

(d) Calculation of IC₅₀.

The enzyme activity was measured in the presence of at least 4 concentrations of each compound. The data were for the 4-pyridyl and 2-picolyl compounds of Table 1 fitted by linear regression to the Dixon equation (M. Dixon, E.C. Webb, Enzymes, 2nd ed., Academic Press, New York, 1964). Data for all the other compounds were fitted by non-linear regression to the median effect equation of Chou, J. Theoret. Biol. 39, 253–276 (1976). The correlation coefficients were greater than 0.95 except for the compound of Example 1, where it was 0.91. All the assays were carried out with approx. 4 nM enzyme (as calculated from kinetic measurements) except those for Ketoconazole and the 2- and 4-pyridyl and 2-picolyl compounds of Table 1, in which 25 nM lyase and 10 nM hydroxylase were used. The IC₅₀ values are dependent on enzyme concentration when the inhibitor binds tightly (all the compounds tested except the 4-pyridyl and 2-picolyl). Results are shown in Table 2 below.

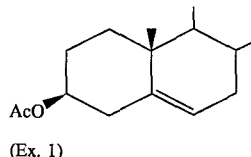
TABLE 2

(a) Confirmation that variations in the A and B rings of compounds of the invention have little effect on inhibition of hydroxylase and lyase.



Compounds tested are of formula (3) wherein R = H:

Q	IC ₅₀ (μ M)	
	Lyase	Hydroxylase
Q	0.0097	0.0130

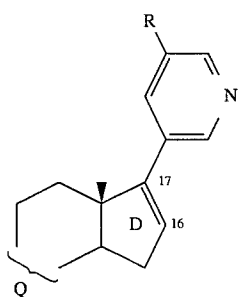
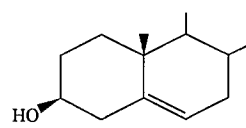
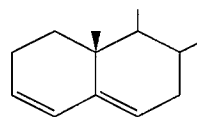
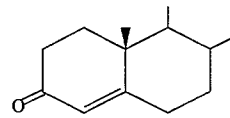
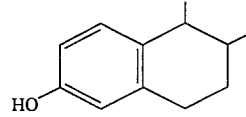
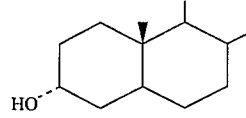
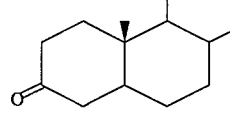


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TABLE 2-continued

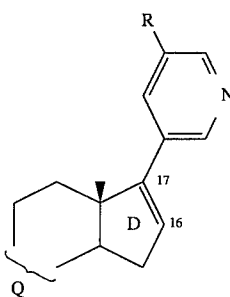
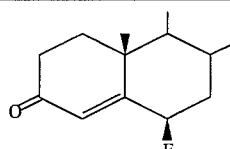
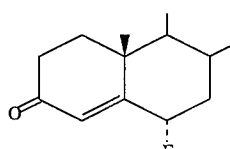
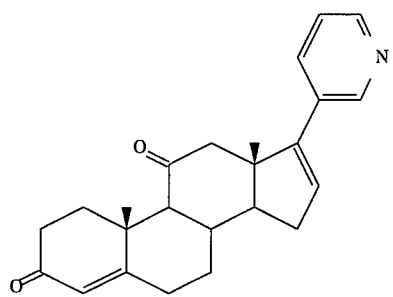
(a) Confirmation that variations in the A and B rings of compounds of the invention have little effect on inhibition of hydroxylase and lyase.

Q	IC ₅₀ (μM)	
	Lyase	Hydroxylase
		
Compounds tested are of formula (3) wherein R = H:		
	0.0029	0.0040
	0.0056	0.0125
	0.0021	0.0028
	0.0018	0.0026
	0.0025	0.0043
	0.0030	0.0047

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TABLE 2-continued

(a) Confirmation that variations in the A and B rings of compounds of the invention have little effect on inhibition of hydroxylase and lyase.

Q	IC ₅₀ (μM)	
	Lyase	Hydroxylase
		
Compounds tested are of formula (3) wherein R = H:		
	0.0022	0.0033
	0.0032	0.0053
(b) Confirmation that variation in the C ring of compounds of the invention has little effect on the inhibition of hydroxylase and lyase.		
Compound Tested		
45	IC ₅₀ (μM)	
	Lyase	Hydroxylase
	0.0025	0.0091
		

The comparative IC₅₀ figures for Ketoconazole are 0.026 against lyase and 0.065 against hydroxylase.
Assay of aromatase activity

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Aromatase activity was determined by the method of A. B. Foster et al., J. Med. Chem. 26, 50-54 (1983), using human placental microsomes. For the microsomes used, the Michaelis constant K_m for [1β - 3 H] androstenedione was 0.039 μ M.

The compounds having a pregnenolone-like skeleton in the A and B rings, i.e. 3β -acetoxy-17-(3-pyridyl)androst-5,16-diene and its 3-alcohol of Examples 1 and 2, had $IC_{50} > 20$ μ M. The compound having a progesterone-like skeleton in the A and B rings, i.e. 17-(3-pyridyl)-androst-4,16-dien-3-one of Example 4 exhibited also aromatase inhibitory activity with $IC_{50} = 1$ μ M.

In vivo organ weight and endocrine test in mice

Male HWT mice, 12 weeks old, were treated daily for 2 weeks, with 5 animals per treatment group. The test compounds were the compound of Examples 1 and 4 (as representative of compounds of the invention having the pregnenolone-like and progesterone-like skeletons respectively). Ketoconazole was also tested at three different doses. The test compounds were made up in 5% benzyl alcohol, 95% safflower oil, and were given i.p. In addition to an untreated control group of animals, there was also a solvent control group which received the same volume of liquid as the test group (5 ml/kg) but no test compound. All animals were sacrificed 24 hours after the last injection. Blood was collected by cardiac puncture into heparinized tubes, and the plasma used for RIA (radio immunoassay) of testosterone and luteinising hormone. The following organs were removed and weighed: adrenals, prostate, seminal vesicles, testes, kidneys. There was no significant body weight loss in any group of mice during the experiments.

Post mortem examination of the mice revealed oil/white deposits i.p. in those treated with compound of Ex. 1 and white deposits throughout the abdomen in those treated with compound of Ex. 4. In all these mice, all organs looked normal. In Ketoconazole-treated animals, adhesions were found in 2/5, 2/5, 4/5 of the low/middle/top dose groups. The gut and peritoneal wall seemed to be stuck to the seminal vesicles. The livers were brown in the middle/top dose groups.

The weights of organs found in the animals post mortem are shown in Table 3 below. The reductions in weight of all of the prostate, seminal vesicles, testes and kidneys were much greater for the test compounds of the invention than for Ketoconazole. Ketoconazole caused an increase in adrenal weight at the two highest doses, whereas the compounds of the invention had no significant effect, suggesting that they did not inhibit corticosterone biosynthesis.

TABLE 3

Mean weight (mg.) \pm standard error					
Dose	Adrenals	Prostate	Seminal Vesicles	Testes	Kidneys
Compound of Ex. 1.					
Controls	4.5 \pm 0.1	10.1 \pm 0.7	189 \pm 9	146 \pm 3	709 \pm 17
Solvent	4.5 \pm 0.4	10.2 \pm 1.3	171 \pm 6	122 \pm 7	615 \pm 28
controls					
0.02 mmol/kg/day	4.3 \pm 0.2	8.0 \pm 0.6	136 \pm 4	134 \pm 4	604 \pm 24
0.1 mmol/kg/day	4.0 \pm 0.2	5.3 \pm 0.3	51 \pm 6	95 \pm 3	500 \pm 8
0.5 mmol/kg/day	4.7 \pm 0.2	5.6 \pm 0.6	25 \pm 2	56 \pm 2	449 \pm 12

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TABLE 3-continued

Mean weight (mg.) \pm standard error					
Dose	Adrenals	Prostate	Seminal Vesicles	Testes	Kidneys
Compound of Ex. 4					
Controls	4.3 \pm 0.4	8.4 \pm 0.2	165 \pm 18	142 \pm 8	652 \pm 45
Solvent	4.4 \pm 0.0	9.2 \pm 0.9	152 \pm 9	122 \pm 8	589 \pm 24
controls					
0.02 mmol/kg/day	4.7 \pm 0.2	5.9 \pm 0.8	108 \pm 4	117 \pm 9	599 \pm 29
0.1 mmol/kg/day	4.6 \pm 0.4	6.4 \pm 0.5	61 \pm 9	105 \pm 5	549 \pm 28
0.5 mmol/kg/day	4.9 \pm 0.1	4.1 \pm 0.5	25 \pm 1	59 \pm 2	468 \pm 15
Ketoconazole					
Controls	4.2 \pm 0.2	8.9 \pm 0.8	193 \pm 8	145 \pm 4	670 \pm 12
Solvent					
controls	4.7 \pm 0.4	9.3 \pm 1.2	198 \pm 18	146 \pm 3	615 \pm 25
0.01 mmol/kg/day	4.8 \pm 0.2	9.1 \pm 0.8	235 \pm 18	141 \pm 5	637 \pm 22
0.225 mmol/kg/day	6.1 \pm 0.3	10.8 \pm 1.4	171 \pm 5	127 \pm 7	574 \pm 23
0.5 mmol/kg/day	6.9 \pm 0.3	9.3 \pm 0.9	179 \pm 20	133 \pm 6	710 \pm 30

The results indicate the inhibition by the components of the invention of androgen and particularly testosterone synthesis. They are confirmed by endocrinological results shown in Table 4.

Although the solvent itself produced marked depression of testosterone levels, probably due to stress on the animals, the further decrease resulting from the administration of test compounds was much more marked for the compounds of the invention than for ketoconazole. The rise in LH levels is ascribed to a feedback mechanism associated with depletion of testosterone.

TABLE 4

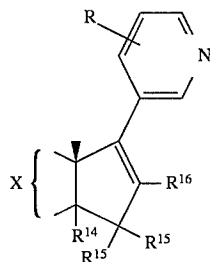
Endocrinological Results (Mean \pm standard error)		
	Testosterone nM	LH ng/ml
Compound of Ex. 1		
Controls	9.8 \pm 5.6	0.63 \pm 0.16
Solvent Controls	2.5 \pm 1.2	0.80 \pm 0.09
0.02 Mmol/Kg/Day	2.7 \pm 0.5	3.4 \pm 0.5
0.1 Mmol/Kg/Day	0.2 \pm 0.1	2.55 \pm 0.45
0.5 Mmol/Kg/Day	0.1 \pm 0.0	2.25 \pm 0.67
Compound of Ex. 4		
Control	27.8 \pm 11.4	Not determined
Solvent Control	11.0 \pm 5.6	Not determined
0.02 Mmol/Kg/Day	4.5 \pm 0.3	Not determined
0.1 Mmol/Kg/Day	3.5 \pm 1.0	Not determined
0.5 Mmol/Kg/Day	0.4 \pm 0.1	Not determined
Ketoconazole		
Controls	17.3 \pm 7.1	0.66 \pm 0.05
Solvent Controls	1.3 \pm 0.4	0.25 \pm 0.13
0.1 Mmol/Kg/Day	0.9 \pm 0.2	0.39 \pm 0.14
0.225 Mmol/Kg/Day	0.7 \pm 0.1	0.75 \pm 0.02
0.5 Mmol/Kg/Day	0.4 \pm 0.1	0.76 \pm 0.03

We claim:

1. A compound of the formula (I)

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wherein X represents the residue of the A, B and C rings of a steroid selected from the group consisting of androstan-3 α - or 3 β -ol, androst-5-en-3 α - or 3 β -ol, androst-4-en-3-one, androst-2-ene, androst-4-ene, androst-5-ene, androsta-5,7-dien-3 α or 3 β -ol, androsta-1,4-dien-3-one, estra-1,3,5[10]-trien-3-ol, 5 α -androstan-3-one, androst-4-ene-3,11-dione, 6-fluoroandrost-4-ene-3-one, androstan-4-ene-3,6-dione, each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters

to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions

as 3-oximes

as 3-methylenes

as 3-carboxylates

as 3-nitriles

as 3-nitros

as 3-desoxy derivatives

to have one or more hydroxy, halo, C₁₋₄-alkyl, trifluoromethyl, C₁₋₄-alkoxy, C₁₋₄-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring

to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

androsta-3,5-diene,

androsta-3,5-diene-3-ol,

estra-1,3,5[10]-triene and

estra-1,3,5[10]-trien-3-ol,

5 α -androstan-3-one;

androst-4-ene-3,11-dione,

6-fluoroandrost-4-ene-3-one,

androstan-4-ene-3,6-dione,

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters

to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions

as 3-oximes

as 3-methylenes

as 3-carboxylates

as 3-nitriles

as 3-nitros

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as 3-desoxy derivatives

to have one or more hydroxy, halo, C₁₋₄-alkyl, trifluoromethyl, C₁₋₄-alkoxy, C₁₋₄-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring

to be 19-nor;

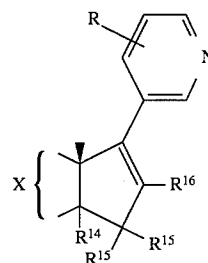
R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

R¹⁴ represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R¹⁵ substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R¹⁴ and one of the R¹⁵ groups together represent a double bond and the other R¹⁵ group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R¹⁶ represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, but excluding 3 β -acetoxy-17-(3-pyridyl)androst-5,14,16-triene, 3 β ,15 α - and 3 β ,15 β -diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3 β -methoxy-17-(3-pyridyl)-5 α -androst-16-ene.

2. A method of treating an androgen-dependent or estrogen-dependent disorder which comprises administering to a patient in a therapeutically effective dose a compound of the formula (1):



wherein X represents the residue of the A, B and C rings of a steroid selected from the group consisting of androstan-3 α - or 3 β -ol, androst-5-en-3 α - or 3 β -ol, androst-4-en-3-one, androst-2-ene, androst-4-ene, androst-5-ene, androsta-5,7-dien-3 α or 3 β -ol, androsta-1,4-dien-3-one, androsta-3,5-diene, androsta-3,5-dien-3-ol, estra-1,3,5[10]-triene and

R¹⁴ represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R¹⁵ substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R¹⁴ and one of the R¹⁵ groups together represent a double bond and the other R¹⁵ group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R¹⁶ represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts.

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3. A compound according to claim 1, which is saturated and unsubstituted at the 11- and 12-positions.

4.

17-(3-Pyridyl)androsta-5,16-dien-3 β -ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5 α -androst-16-en-3 α -ol
and their acid addition salts and 3-esters.

5. A compound according to claim 1 wherein R represents a hydrogen atom.

6.

17-(3-Pyridyl)-5 α -androst-16-en-3-one,
17-(3-pyridyl)-androsta-4,16-diene-3,11-dione,
17-(3-pyridyl)-androsta-3,5,16-trien-3-ol,
6 α - and 6 β -fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)androsta-4,16-dien-3,6-dione,
3 α -trifluoromethyl-17-(3-pyridyl)androst-16-en-3 β -ol
and their acid addition salts and 3-esters.

7. 3 β -Alkanoyloxy-17-(3-pyridyl)androsta-5,16-dienes in which the alkanoyloxy group has from 2 to 4 carbon atoms.

8. 3 β -Acetoxy-17-(3-pyridyl)androsta-5,16-diene.

9. A pharmaceutical composition comprising a compound of claim 1 in association with a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition comprising a compound of claim 3 in association with a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition comprising a compound of claim 1 wherein R represent a hydrogen atom in association with a pharmaceutically acceptable carrier or diluent.

12. A pharmaceutical composition comprising a compound of claim 4 in association with a pharmaceutically acceptable carrier or diluent.

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13. A pharmaceutical composition comprising a compound of claim 6 in association with a pharmaceutically acceptable carrier or diluent.

14. A pharmaceutical composition comprising a compound of claim 7 in association with a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising a compound of claim 8 in association with a pharmaceutically acceptable carrier or diluent.

16. A method according to claim 2 wherein the patient has prostatic cancer.

17. A method according to claim 2 wherein the patient has breast cancer.

18. A method according to claim 2 wherein the compound defined in claim 2 is saturated and unsubstituted at the 11- and 12-positions.

19. A method according to claim 2 wherein the compound is selected from the group consisting of:

17-(3-pyridyl)androsta-5,16-dien-3 β -ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5 α -androst-16-en-3 α -ol
and their acid addition salts and 3-esters.

20. A method according to claim 2 wherein the compound is a 3 β -alkanoyloxy-17-(3-pyridyl)androsta-5,16-diene wherein the alkanoyloxy group has 2 to 4 carbon atoms.

21. A method according to claim 2 wherein the compound is 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene.

22. An orally ingestible solid composition or a sterile injectable liquid composition comprising respectively a solid or liquid pharmaceutically acceptable carrier or diluent and a compound as defined by general formula (1) of claim 2.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

Page 1 of 2

PATENT NO. : 5,604,213
DATED : February 18, 1997
INVENTOR(S) : Barrie, et. al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27, lines 22-46, delete "estra-1,3,5[10]-trien-3-ol ... R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;"

Column 28, line 52, insert --,-- after "estra-1,3,5[10]-triene"

Column 28, line 52, insert the following after "estra-1,3,5[10]-triene,"

--estra-1,3,5[10]-trien-3-ol,

5 α -androstan-3-one,

androst-4-ene-3,11-dione,

6-fluoroandrost-4-ene-3-one,

androstan-4-ene-3,6-dione,

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

Page 2 of 2

PATENT NO. : 5,604,213
DATED : February 18, 1997
INVENTOR(S) : Barrie, et. al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions

as 3-oximes

as 3-methylenes

as 3-carboxylates

as 3-nitriles

as 3-nitros

as 3-desoxy derivatives

to have one or more hydroxy, halo, C₁₋₄-alkyl, trifluoromethyl, C₁₋₄-alkoxy, C₁₋₄-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B or C-ring

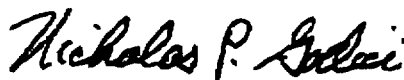
to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

Signed and Sealed this

Twenty-seventh Day of February, 2001

Attest:



NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

EXHIBIT B



US008822438B2

(12) **United States Patent**
Auerbach et al.

(10) **Patent No.:** **US 8,822,438 B2**
(45) **Date of Patent:** **Sep. 2, 2014**

(54) **METHODS AND COMPOSITIONS FOR TREATING CANCER**

(75) Inventors: **Alan H. Auerbach**, Hermosa Beach, CA (US); **Arie S. Beldegrum**, Los Angeles, CA (US)

(73) Assignee: **Janssen Oncology, Inc.**, Los Angeles, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/034,340**

(22) Filed: **Feb. 24, 2011**

(65) **Prior Publication Data**

US 2011/0144016 A1 Jun. 16, 2011

Related U.S. Application Data

(63) Continuation of application No. 11/844,440, filed on Aug. 24, 2007, now abandoned.

(60) Provisional application No. 60/921,506, filed on Aug. 25, 2006.

(51) **Int. Cl.**

A61K 31/56 (2006.01)

A61K 31/58 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/58** (2013.01)

USPC **514/170**; **514/180**

(58) **Field of Classification Search**

USPC **514/170**, **182**
See application file for complete search history.

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Primary Examiner — San-Ming Hui

(57) **ABSTRACT**

Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17 α -hydroxylase/C_{17,20}-lyase inhibitor, such as abiraterone acetate (i.e., 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene), in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17 α -hydroxylase/C_{17,20}-lyase inhibitor, and at least one additional therapeutic agent, such as an anti-cancer agent or a steroid.

20 Claims, No Drawings

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METHODS AND COMPOSITIONS FOR TREATING CANCER

FIELD OF THE INVENTION

Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate (i.e., 3β -acetoxy-17-(3-pyridyl) androsta-5,16-diene), in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, and at least one additional therapeutic agent such as an anti-cancer agent or a steroid, e.g., a corticosteroid or, more specifically, a glucocorticoid.

BACKGROUND

The number of people diagnosed with cancer has significantly increased. Of special interest are individuals diagnosed with androgen-dependent disorders, such as prostate cancer, and estrogen-dependent disorders, such as breast cancer since such diagnoses are increasing in number at an alarming rate.

Prostate cancer is currently the most common non-skin cancer and the second leading cause of cancer-related death in men after lung cancer. The primary course of treatment for patients diagnosed with organ-confined prostate cancer is usually prostatectomy or radiotherapy. Not only are these treatments highly invasive and have undesirable side effects, such localized treatments are not effective on prostate cancer after it has metastasized. Moreover, a large percent of individuals who receive localized treatments will suffer from recurring cancer.

Additionally, breast cancer incidence in women has increased from one out of every 20 women in 1960 to one out of every eight women in 2005. Moreover, it is the most common cancer among white and African-American women. Similar to treating prostate cancer, most options for women diagnosed with breast cancer are highly invasive and have significant side-effects. Such treatments include surgery, radiation and chemotherapy.

Hormone therapy is another treatment option for individuals diagnosed with prostate or breast cancer. Hormone therapy is a form of systemic treatment for prostate or breast cancer wherein hormone ablation agents are used to suppress the production or block the effects of hormones, such as estrogen and progesterone in the body, which are believed to promote the growth of breast cancer, as well as testosterone and dihydrotestosterone, which are believed to promote the growth of prostate cancer. Moreover, hormone therapy is less invasive than surgery and does not have many of the side effects associated with chemotherapy or radiation. Hormone therapy can also be used by itself or in addition to localized therapy and has shown to be effective in individuals whose cancer has metastasized.

Even though hormone therapy is less invasive and can be used on more advanced stages of cancer, some individuals administered current hormone therapy treatments may not show a significant response or may not show any response at all to such treatments. Additionally, some patients treated with current hormone therapy treatments may also suffer from relapsing or recurring cancer. Currently, such refractory cancer patients are left with very few treatment options.

Despite the progress made in the treatment of cancer, there remains a need for more effective ways to treat cancer such as, but not limited to, prostate cancer and breast cancer. Addi-

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tionally, there is a need for effective anti-cancer treatment options for patients who are not responding to current anti-cancer treatments. Also, there is a need for effective anti-cancer treatment options for patients whose cancer has recurred.

SUMMARY OF THE INVENTION

Described herein are methods for treating a cancer in which a therapeutically effective amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate (i.e. 3β -acetoxy-17-(3-pyridyl)androsta-5,16-diene), is administered to a patient, e.g., a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent or steroid. Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, in certain embodiments, the method is directed to treating a refractory cancer in a patient, in which a therapeutically effective amount of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered to a patient currently receiving an anti-cancer agent.

For example, in certain embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 mg/m² to about 20 mg/m² of mitoxantrone.

In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 175 mg/m² of paclitaxel.

In still other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 100 mg/m² of docetaxel.

Furthermore, described herein is a method for the treatment of a cancer in a mammal comprising administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate; and an amount of about 0.01 mg to about 200 mg of leuprolide, wherein the leuprolide is administered over a period of about 3 days to about 12 months.

In other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of goserelin, wherein the goserelin is administered over a period of about 28 days to about 3 months.

Additionally, in another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of triptorelin, wherein the triptorelin is administered over a period of about 1 month.

The method for the treatment of a cancer in a mammal can also comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 µg/day to about 500 µg/day of seocalcitol, such as about 100 µg/day of seocalcitol.

Also, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

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In yet another embodiment, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone.

Also described herein are compositions for the treatment of cancer that comprise a combination of a therapeutically effective amount of at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and a therapeutically effective amount of at least one additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including, but not limited to, hydrocortisone, prednisone, or dexamethasone.

Finally, single unit dosage forms comprising abiraterone acetate and a glucocorticoid, optionally with carriers, diluents or excipients, are contemplated. Also, kits comprising at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and an additional anti cancer agent or steroid are contemplated. For example, the kit may include a vial containing abiraterone acetate and another vial containing a glucocorticoid.

DEFINITIONS

As used herein and unless otherwise defined the word “cancer,” refers to the growth, division or proliferation of abnormal cells in the body. Cancers that can be treated with the methods and the compositions described herein include, but are not limited to, prostate cancer, breast cancer, adrenal cancer, leukemia, lymphoma, myeloma, Waldenström’s macroglobulinemia, monoclonal gammopathy, benign monoclonal gammopathy, heavy chain disease, bone and connective tissue sarcoma, brain tumors, thyroid cancer, pancreatic cancer, pituitary cancer, eye cancer, vaginal cancer, vulvar cancer, cervical cancer, uterine cancer, ovarian cancer, esophageal cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, lung cancer, testicular cancer, penial cancer, oral cancer, skin cancer, kidney cancers, Wilms’ tumor and bladder cancer.

As used herein, and unless otherwise defined, the terms “treat,” “treating” and “treatment” include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

As used herein, and unless otherwise defined, the term “patient” means an animal, including but not limited to an animal such as a human, monkey, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig. In one embodiment, the patient is a mammal and in another embodiment the patient is a human. In certain embodiments, the patient can be an adult male or female. In some embodiments, the patient is a male of age about 30 years to about 85 years. In other embodiments, the patient is a female of age about 30 years to about 85 years. In a particular embodiment, the patient has or is susceptible to having (e.g., through genetic or environmental factors) cancer. In a further embodiment, the patient has or is susceptible to having (e.g., through genetic or environmental factors) a tumor. In other embodiments, the patient can be castrated or non-castrated.

The term “ 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor” as used herein refers to an inhibitor of 17α -hydroxylase/ $C_{17,20}$ -

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lyase, (which is an enzyme in testosterone synthesis), an analog thereof, derivative thereof, metabolite thereof or pharmaceutically acceptable salt thereof. Also, unless otherwise noted, reference to a particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can include analogs, derivatives, metabolites or pharmaceutically acceptable salts of such particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

The term “anti-cancer agent” as used herein refers to any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells. It should be noted that even though throughout this specification and in the claims the phrase “anti-cancer agent” is written as a singular noun, for example; “an anti-cancer agent” or “the anti-cancer agent,” the phrase “anti-cancer agent” should not be interpreted as being limited to the inclusion of a single anti-cancer agent.

As used herein, and unless otherwise defined, the phrase “therapeutically effective amount” when used in connection with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent means an amount of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.

As used herein and unless otherwise defined the phrase “refractory cancer,” means cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

As used herein and unless otherwise defined the phrase “refractory patient,” means a patient who has refractory cancer.

As used herein and unless otherwise defined the phrase “relapse cancer,” means cancer that was at one time responsive to an anti-cancer treatment but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

As used herein and unless otherwise defined the phrase “recurring cancer,” means cancer that has returned after a patient has been earlier diagnosed with cancer, under gone treatment or had been previously diagnosed as cancer-free.

As used herein and unless otherwise defined the term “derivative” refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound. The derivative may retain or improve the pharmacological activity of the compound from which it is derived.

As used herein and unless otherwise defined the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

As used herein and unless otherwise defined the phrase “pharmaceutically acceptable salt” refers to any salt of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor which retains the biological effectiveness of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor. Examples of pharmaceutically acceptable salts include, but are not limited to, acetates, sulfates, pyrosulfates, bisulfates, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phylacetates, phenylpropionates, phenylbutyrate, citrates, lactates, gamma-hydroxybutyrate,

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glycollates, tartarates, alkanesulfonates (e.g. methane-sulfonate or mesylate), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. Several of the officially approved salts are listed in Remington: The Science and Practice of Pharmacy, Mack Publ. Co., Easton.

DETAILED DESCRIPTION OF THE INVENTION

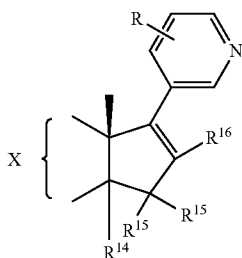
The methods described herein for treating cancer comprise administering to a mammal, preferably a human, a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor in addition to at least one therapeutic agent, such as an anti-cancer agent or steroid, particularly a glucocorticoid. The compositions described herein comprise a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and at least one additional therapeutic agent, such as an anti-cancer agent or steroid, particularly a corticosteroid or glucocorticoid. Other anti-cancer treatments such as, administration of yet another anti-cancer agent, radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy, can be used with the methods and compositions.

 17α -Hydroxylase/ $C_{17,20}$ -Lyase Inhibitors

17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors have been shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer respectively, as described in U.S. Pat. No. 5,604,213 to Barrie et al., which is herein incorporated by reference in its entirety.

In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be 17-(3-pyridyl)androsta-5,16-dien-3 β ol; 17-(3-pyridyl)androsta-3,5,16-triene; 17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol; 17-(3-pyridyl)-5 α -androst-16-en-3 α -ol; 17-(3-pyridyl)-5 α -androst-16-en-3-one; 17-(3-pyridyl)-androsta-4,16-diene-3,11-dione; 17-(3-pyridyl)-androsta-3,5,16-trien-3-ol; 6 α - and 6 β -fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)androsta-4,16-dien-3,6-dione; 3 α -trifluoromethyl-17-(3-pyridyl)androst-16-en-3 β -ol or their acid addition salts and 3-esters as well as metabolites, analogs, derivatives or a pharmaceutically acceptable salt thereof.

In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can have the structure of formula (I):



wherein X represents the residue of the A, B and C rings of a steroid which can be, without limitation, androstan-3 α - or 3 β -ol; androst-5-en-3 β - or 3 β -ol; androst-4-en-3-one; androst-2-ene; androst-4-ene; androst-5-ene; androsta-5,7-dien-3 α or 3 β -ol; androsta-1,4-dien-3-one; androsta-3,5-diene; androsta-3,5-diene-3-ol; estra-1,3,5[10]-triene; estra-1,3,5[10]-trien-3-ol; 5 α -androstan-3-one; androst-4-ene-3,11-dione; 6-fluoroandrost-4-ene-3-one; or androstan-4-ene-3,6-dione; each of which, where structurally permissible, can be further derivatized in one or more of the following ways, including, but not limited to, to form 3-esters; to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions; as 3-oximes; as 3-methylenes; as 3-carboxylates; as 3-nitriles; as 3-nitros; as

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3-desoxy derivatives; to have one or more hydroxy, halo, C_{1-4} -alkyl, trifluoro-methyl, C_{1-4} -alkoxy, C_{1-4} -alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring; or to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

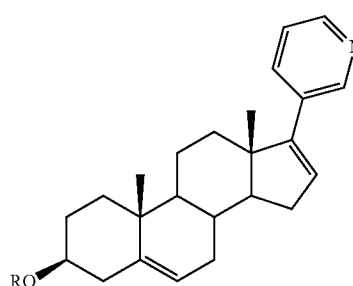
R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, but excluding 3 β -acetoxy-17-(3-pyridyl)androsta-5,14,16-triene, 3 β ,15 α - and 3 β ,15 β -diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3 β -methoxy-17-(3-pyridyl)-5 α -androst-16-ene.

Suitable inhibitors also include metabolites, derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

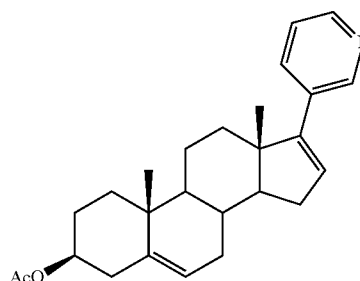
In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can have the structure of formula (I):



wherein R represents hydrogen or a lower acyl group having 1 to 4 carbons. Suitable inhibitors also include derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

In still another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be a 3 β -alkanoyloxy-17-(3-pyridyl)androsta-5,16-diene in which the alkanoyloxy group has from 2 to 4 carbon atoms.

In a preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor comprises abiraterone acetate or 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene which has the following structural formula:

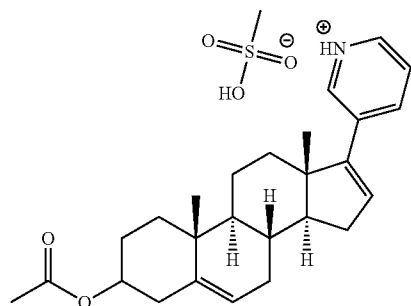


and pharmaceutically acceptable salts thereof.

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Preferred salts of abiraterone acetate and methods of making such salts are also disclosed in U.S. Provisional Application No. 60/603,559 to Hunt, which is incorporated by reference in its entirety. Preferred salts include, but are not limited to, acetates, citrates, lactates, alkane-sulfonates (e.g. methane-sulfonate or mesylate) and tartarates. Of special interest is the abiraterone acetate mesylate salt (i.e. 3β -acetoxy-17-(3-pyridyl)androst-5,16-diene mesylate salt) which has the following structural formula:



The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors can be made according to any method known to one skilled in the art. For example, such inhibitors can be synthesized according to the method disclosed in U.S. Pat. Nos. 5,604,213 and 5,618,807 to Barrie et al., herein incorporated by reference. Another method of making 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors is disclosed in U.S. provisional application 60/603,558 to Bury, herein incorporated by reference.

The amount of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer, whether the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered alone or in combination with an additional anti-cancer treatment, such as an additional anti-cancer agent.

Additional Therapeutic Agents

Suitable compounds that can be used in addition to 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors as an anti-cancer agent include, but are not limited to, hormone ablation agents, anti-androgen agents, differentiating agents, anti-neoplastic agents, kinase inhibitors, anti-metabolite agents, alkylating agents, antibiotic agents, immunological agents, interferon-type agents, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, mitotic inhibitors, matrix metalloprotease inhibitors, genetic therapeutics, and anti-androgens. The amount of the additional anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor. Below are lists of examples of some of the above classes of anti-cancer agents. The examples are not all inclusive and are for purposes of illustration and not for purposes of limitation. Many of the examples below could be listed in multiple classes of anti-cancer agents and are not restricted in any way to the class in which they are listed in.

Suitable hormonal ablation agents include, but are not limited to, androgen ablation agents and estrogen ablation agents. In preferred embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered with a hormonal ablation agent, such as deslorelin, leuprolide, goserelin or triptorelin. Even though throughout this specification and in the claims the phrase "hormonal ablation agent" is written as a

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singular noun, for example; "a hormonal ablation agent" or "the hormonal ablation agent," the phrase "hormonal ablation agent" should not be interpreted as being limited to the inclusion of a single hormonal ablation agent. The amount of the hormonal ablation agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

Suitable anti-androgen agents include but are not limited to bicalutamide, flutamide and nilutamide. The amount of the anti-androgen agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with a differentiating agent. Suitable differentiating agents include, but are not limited to, polyamine inhibitors; vitamin D and its analogs, such as, calcitriol, doxercalciferol and seocalcitol; metabolites of vitamin A, such as, ATRA, retinoic acid, retinoids; short-chain fatty acids; phenylbutyrate; and nonsteroidal anti-inflammatory agents. The amount of the differentiating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

In another preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-neoplastic agent, including, but not limited to, tubulin interacting agents, topoisomerase inhibitors and agents, acitretin, alstonine, amonafide, amphethinile, amsacrine, ankinomycin, anti-neoplaston, aphidicolin glycinate, asparaginase, baccharin, batracylin, benfluron, benzotript, bromofosfamide, caracemide, carmethizole hydrochloride, chlorsulfaquinolone, clafenur, claviridenone, crinamol, cytarabine, cytosytin, dacarbazine, datelliptinium, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, docetaxel, elliprabine, elliptinium acetate, epothilones, ergotamine, etoposide, etretinate, fenretinide, gallium nitrate, genkwadaphnin, hexadecylphosphocholine, homoharringtonine, hydroxyurea, ilmofofine, isoglutamine, isotretinoin, leukoregulin, lonidamine, merbarone, merocyanine derivatives, methylalnilinoacridine, minactivin, mitonafide, mitouidone, mitoxantrone, mopidamol, motretinide, N-(retinoyl)amino acids, N-acylated-dehydroalanines, nafazatrom, nocodazole derivative, ocreotide, oquizanocine, paclitaxel, pancratistatin, pazelliptine, piroxantrone, polyhaematoporphyrin, polypreic acid, probimane, procarbazine, proglumide, razoxane, retelliptine, spatol, spirocyclopropane derivatives, spirogermanium, strypoldinone, superoxide dismutase, teniposide, thaliblastine, tocotrienol, topotecan, ukrain, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, and withanolides. The amount of the anti-neoplastic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be used with a kinase inhibitor including p38 inhibitors and CDK inhibitors, TNF inhibitors, metalloproteinases inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics or $\alpha_v\beta_3$ inhibitors. The amount of the kinase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-metabolite agent.

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Suitable anti-metabolite agents may be selected from, but not limited to, 5-FU-fibrinogen, acanthifolic acid, aminothiadia-
zole, brequinar sodium, carmofur, cyclopentyl cytosine, cy-
tarabine phosphate stearate, cytarabine conjugates, dezagua-
nine, dideoxycytidine, dideoxyguanosine, didox,
doxifluridine, fazarabine, floxuridine, fludarabine phosphate,
5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, isopropyl
pyrrolizine, methobenzaprim, methotrexate, norspermidine,
pentostatin, piritrexim, plicamycin, thioguanine, tiazofurin,
trimetrexate, tyrosine kinase inhibitors, and uracitin. The
amount of the anti-metabolite agent administered to a mam-
mal having cancer is an amount that is sufficient to treat the
cancer whether administered alone or in combination with a
17 α -hydroxylase/C_{17,20}-lyase inhibitor.

In another embodiment, the 17 α -hydroxylase/C_{17,20}-lyase
inhibitor may be administered with an alkylating agent. Suit-
able alkylating agents may be selected from, but not limited
to, aldo-phosphamide analogues, altretamine, anaxirone,
bestrabucil, budotitane, carboplatin, carmustine, chloram-
bucil, cisplatin, cyclophosphamide, cyplatate, diphenylspiro-
mustine, diplatinum cytostatic, elmustine, estramustine phos-
phate sodium, fotemustine, hepsul-fam, ifosfamide,
iproplatin, lomustine, mafosfamide, mitolactol, oxaliplatin,
prednimustine, ranimustine, semustine, spiromustine, tauro-
mustine, temozolomide, teroxirone, tetraplatin and trim-
elamol. The amount of the alkylating agent administered to
a mammal having cancer is an amount that is sufficient to treat
the cancer whether administered alone or in combination with
a 17 α -hydroxylase/C_{17,20}-lyase inhibitor.

In another preferred embodiment, the 17 α -hydroxylase/
C_{17,20}-lyase inhibitor may be administered with an antibiotic
agent. Suitable antibiotic agents may be selected from, but not
limited to, aclarubicin, actinomycin D, actinoplanone, adria-
mycin, aeropylsinin derivative, amrubicin, anthracycline,
azino-mycin-A, bisucaberin, bleomycin sulfate, bryostatin-1,
caliche mycin, chromoximycin, dactinomycin, daunorubicin,
ditrisarubicin B, dexamethasone, doxorubicin, doxorubicin-
fibrinogen, elsamycin-A, epirubicin, erbstatin, esorubicin,
esperamicin-A1, esperamicin-A1b, fostriecin, glidobactin,
gregatin-A, grincamycin, herbimycin, corticosteroids such as
hydrocortisone, idarubicin, illudins, kzusamycin, kesarirho-
dins, menogaril, mitomycin, neoactin, oxalysine, oxauno-
mycin, peplomycin, pilatin, pirarubicin, porothramycin,
prednisone, prednisolone, pyridandycin A, rapamycin,
rhizoxin, rodorubicin, sibanomicin, siwenmycin, sorangicin-
A, sparsomycin, talisomycin, terpenecin, thrazine, tric-
rozarin A, and zorubicin. The amount of the antibiotic agent
administered to a mammal having cancer is an amount that is
sufficient to treat the cancer whether administered alone or in
combination with a 17 α -hydroxylase/C_{17,20}-lyase inhibitor.

Alternatively, the 17 α -hydroxylase/C_{17,20}-lyase inhibitors
may also be used with other anti-cancer agents, including but
not limited to, acemannan, aclarubicin, aldesleukin, alemtu-
zumab, alitretinoin, altretamine, amifostine, amsacrine,
anagrelide, anastrozole, aneastim, bexarotene, broxuridine,
capecitabine, celmoleukin, cetorelix, cladribine, clotrima-
zole, daclizumab, dexrazoxane, dilazep, docosanol, doxiflu-
ridine, bromocriptine, carmustine, cytarabine, diclofenac,
edelfosine, edrecolomab, eflornithine, emitefur, exemestane,
exisulind, fadrozole, filgrastim, finasteride, fludarabine phos-
phate, formestane, fotemustine, gallium nitrate, gemcitabine,
glycopine, heptaplatin, ibandronic acid, imiquimod, ioben-
guane, irinotecan, irsogladine, lanreotide, leflunomide,
lenograstim, lentinan sulfate, letrozole, liarozole, lobaplatin,
lonidamine, masoprocol, melarsoprol, metoclopramide,
mifepristone, miltefosine, mirimostim, mitoguazone, mito-
lactol, molgramostim, nafarelin, nartogastim, nedaplatin,

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nilutamide, noscapine, oprelvekin, osaterone, oxaliplatin,
pamidronic acid, pegaspargase, pentosan polysulfate sodium,
pentostatin, picibanil, pirarubicin, porfimer sodium, ralox-
ifene, raltitrexed, rasburicase, rituximab, romurtide, sarga-
mostim, sizofiran, sobuzoxane, sonermin, suramin, tasoner-
min, tazarotene, tegafur, temoporfin, temozolomide,
teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin,
thyrotropin alfa, topotecan, toremifene, trastuzumab, treosul-
fan, tretinoin, trilostane, trimetrexate, ubenimex, valrubicin,
verteporfin, vinorelbine. The amount of the anti-cancer agent
administered to a mammal having cancer is an amount that is
sufficient to treat the cancer whether administered alone or in
combination with a 17 α -hydroxylase/C_{17,20}-lyase inhibitor.

The 17 α -hydroxylase/C_{17,20}-lyase inhibitors may also be
administered or combined with steroids, such as corticoste-
roids or glucocorticoids. The 17 α -hydroxylase/C_{17,20}-lyase
inhibitors and the steroid may be administered in the same or
in different compositions. Non-limiting examples of suitable
steroids include hydrocortisone, prednisone, or dexametha-
sone. The amount of the steroid administered to a mammal
having cancer is an amount that is sufficient to treat the cancer
whether administered alone or in combination with a 17 α -
hydroxylase/C_{17,20}-lyase inhibitor.

In one embodiment, provided herein are methods and com-
positions comprising both abiraterone acetate and a steroid
particularly a corticosteroid, or more particularly a glucocor-
ticoid. Steroids within the scope of the disclosure include, but
are not limited to, (1) hydrocortisone (cortisol; cypionate
(e.g., CORTEF), oral; sodium phosphate injection (HYDRO-
CORTONE PHOSPHATE); sodium succinate (e.g., A-HY-
DROCORT, Solu-CORTEF); cortisone acetate oral or injec-
tion forms, etc.), (2) dexamethasone (e.g., Decadron, oral;
Decadron-LA injection, etc.), (3) prednisolone (e.g., Delta-
CORTEF, prednisolone acetate (ECONOPRED), predniso-
lone sodium phosphate (HYDELTRASOL), prednisolone
tebutate (HYDELTRA-TBA, etc.)), or (4) prednisone DEL-
TASONE, etc.) and combinations thereof. See, e.g., GOODMAN
& GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10TH
EDITION 2001.

In a specific embodiment, single unit solid oral dosage
forms which comprise an amount from about 50 mg to about
300 mg of abiraterone acetate and an amount from about 0.5
mg to about 3.0 mg of a steroid, e.g., glucocorticoid in a single
composition, optionally with excipients, carriers, diluents,
etc. is contemplated. For instance, the single unit dosage form
can comprise about 250 mg of abiraterone acetate and about
1.0 mg, 1.25 mg, 1.5 mg, or 2.0 mg of a steroid, such as but not
limited to corticosteroids or glucocorticoids.

Administration of the 17 α -Hydroxylase/C_{17,20}-Lyase Inhibi-
tor and an Additional Therapeutic Agent

The 17 α -hydroxylase/C_{17,20}-lyase inhibitor and the addi-
tional therapeutic agent, such as an anti-cancer agent or a
steroid can be administered by any method known to one
skilled in the art. In certain embodiments, the 17 α -hydroxy-
lase/C_{17,20}-lyase inhibitor and the additional therapeutic
agent can be in separate compositions prior to administration.
In the alternative, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor
and the additional therapeutic agent can be combined into a
single composition for administration.

The 17 α -hydroxylase/C_{17,20}-lyase inhibitor and the addi-
tional therapeutic agent can be administered sequentially or
simultaneously. If administered sequentially, the order of
administration is flexible. For instance, 17 α -hydroxylase/
C_{17,20}-lyase inhibitor acetate can be administered prior to
administration of the additional therapeutic agent. Alterna-

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tively, administration of the additional therapeutic agent can precede administration of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

Whether they are administered as separate compositions or in one composition, each composition is preferably pharmaceutically suitable for administration. Moreover, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the therapeutic agent, if administered separately, can be administered by the same or different modes of administration. Examples of modes of administration include parenteral (e.g., subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, intradental, intraperitoneal, intraportal, intraarterial, intrathecal, transmucosal, intra-articular, and intrapleural), transdermal (e.g., topical), epidural, and mucosal (e.g., intranasal) injection or infusion, as well as oral, inhalation, pulmonary, and rectal administration. In specific embodiments, both are oral.

For example, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered transdermally and the additional therapeutic agent can be administered parenterally. Alternatively, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered orally, such as in a tablet, caplet or capsule, while the additional therapeutic agent can be administered intravenously. Such intravenous administered therapeutic agents include, but are not limited to, docetaxel injections, such as Taxotere®; paclitaxel injections, such as Paclitaxel® and mitoxantrone injections, such as Novantrone®. Also, the additional therapeutic agent can be in the form of depots or implants such as leuprolide depots and implants, e.g. Viadur® and Lupron Depot®; triptorelin depots, e.g. Trelstar®; goserelin implants, e.g. Zoladex®.

The suitable daily dosage of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor depends upon a number of factors, including, the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, and response of the individual patient. Suitable daily dosages of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day, or from about 0.001 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 100 mg/kg/day in single or multiple doses.

In some embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered in an amount from about 0.004 mg/day to about 5,000 mg/day, or from about 0.04 mg/day to about 3,000 mg/day, or from about 0.4 mg/day to about 1500 mg/day. In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered in an amount from about 0.1 mg/day to about 2000 mg/day or from about 1 mg/day to about 2000 mg/day or from about 50 mg/day to about 2000 mg/day or from about 100 mg/day to about 1500 mg/day or from about 5 mg/day to about 1,000 mg/day or from about 5 mg/day to about 900 mg/day or from about 10 mg/day to about 800 mg/day or from about 15 mg/day to about 700 mg/day or from about 20 mg/day to about 600 mg/day or from about 25 mg/day to about 500 mg/day in single or multiple doses.

In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is co-administered with an additional anti-cancer agent such as mitoxantrone, paclitaxel or docetaxel. For example, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of mitoxantrone. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the mitoxantrone can be administered in an amount of about 0.1 mg/m² to about 20

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mg/m². Preferably, the mitoxantrone is administered over a period of between about 10 to about 20 minutes once every 21 days.

Also, a method for the treatment of a cancer in a mammal can comprise administering an amount of abiraterone acetate and an amount of paclitaxel. In one embodiment, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the paclitaxel can be administered in the amount of about 1 mg/m² to about 175 mg/m². Preferably, the paclitaxel is administered over a period of between about 2 to about 5 hours once every three months.

Additionally, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of docetaxel. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the docetaxel can be administered in an amount of about 1 mg/m² to about 100 mg/m². Preferably, the docetaxel is administered over a period of between about 1 to about 2 hours once every three weeks.

In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered along with an anti-cancer agent that comprises a hormonal ablation agent, including, but not limited to, leuprolide, goserelin, or triptorelin. For example, one method for the treatment of a cancer in a mammal also comprises administering an amount of abiraterone acetate and an amount of leuprolide. The amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of leuprolide can be about 0.01 mg to about 200 mg over a period of about 3 days to about 12 months. Preferably, the leuprolide is administered in the amount of about 3.6 mg of leuprolide over a period of about 3 days to about 12 months.

Additionally, the methods for the treatment of cancer in a mammal include administering an amount of abiraterone acetate and an amount of goserelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of goserelin can be about 0.01 mg to about 20 mg over a period of about 28 days to about 3 months. Preferably, the goserelin is administered in the amount of about 3.6 mg to about 10.8 mg over a period of about 28 days to about 3 months.

In certain embodiments the methods for the treatment of cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of triptorelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of triptorelin can be about 0.01 mg to about 20 mg, over a period of about 1 month, preferably the triptorelin is administered in the amount of about 3.75 mg over a period of about 1 month.

Also, in one embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of seocalcitol. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 µg/day to about 500 µg/day of seocalcitol, such as about 100 µg/day of seocalcitol.

In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of bicalutamide. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

In yet another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of

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abiraterone acetate and an amount of flutamide. For example, the method comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor such as abiraterone acetate and an amount of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of hydrocortisone. In other instances, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of hydrocortisone.

The method for the treatment of a cancer can also comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as prednisone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of prednisone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of prednisone.

In addition, the method for the treatment of a cancer can also comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of dexamethasone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 0.5 mg/day to about 25 mg/day of dexamethasone.

Compositions Containing a 17α -Hydroxylase/ $C_{17,20}$ -Lyase Inhibitor and an Additional Therapeutic Agent

In certain embodiments, the compositions can contain a combination of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, preferably abiraterone acetate, and any of the therapeutic agents recited above. Whether the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent are administered in separate compositions or as a single composition, the compositions can take various forms. For example, the compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders or sustained-release formulations, depending on the intended route of administration.

For topical or transdermal administration, the compositions can be formulated as solutions, gels, ointments, creams, suspensions or salves.

For oral administration, the compositions may be formulated as tablets, pills, dragees, troches, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

The composition may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas that contain conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the composition may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly)

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or by intramuscular injection. Thus, for example, the therapeutic agents may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Additionally, the composition may be delivered using a sustained-release system, such as semi-permeable matrices of solid polymers containing the composition. Various forms of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature can release the composition over a period of hours, days, weeks, months. For example a sustained release capsule can release the compositions over a period of 100 days or longer. Depending on the chemical nature and the biological stability of the composition, additional strategies for stabilization may be employed.

The compositions can further comprise a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered.

For parenteral administrations, the composition can comprise one or more of the following carriers: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

For oral solid formulations suitable carriers include fillers such as sugars, e.g., lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, fats and oils; granulating agents; and binding agents such as microcrystalline cellulose, gum tragacanth or gelatin; disintegrating agents, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate, Primogel, or corn starch; lubricants, such as magnesium stearate or Sterotes; glidants, such as colloidal silicon dioxide; a sweetening agent, such as sucrose or saccharin; or flavoring agents, such as peppermint, methyl salicylate, or orange flavoring. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy injectability with a syringe. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents,

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for example, sugars; polyalcohols such as mannitol, sorbitol; sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Also for intravenous administration, the compositions may be formulated in solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In a preferred embodiment, the compositions are formulated in sterile solutions.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

For administration by inhalation, the compositions may be formulated as an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the composition and a suitable powder base such as lactose or starch.

The pharmaceutical compositions may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

One example of a composition comprising a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and an additional therapeutic agent is an oral composition or composition suitable for oral administration comprising abiraterone acetate in combination with a steroid. For example, the oral composition can be a solid dosage form such as a pill, a tablet or a capsule. The oral composition can comprise about 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of abiraterone acetate. The oral composition can comprises about 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 7.5 mg, 10 mg, 20 mg, 30 mg, 40 mg or 50 mg of a steroid, such as a glucocorticoid.

In one embodiment, the oral composition can comprise about 50 mg to about 500 mg of abiraterone acetate and an amount of about 0.25 mg to about 3.5 mg of the steroid, such as hydrocortisone, prednisone or dexamethasone. In other instances, the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and an amount of about 1.0 mg to about 2.5 mg of the steroid, such as hydrocortisone, prednisone or dexamethasone. In another embodiment the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and about 0.5 mg to about 3.0 mg of a steroid. For example, the oral composition can be a tablet containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients. Additionally, the oral composition can be a capsule containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg

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of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients.

The description contained herein is for purposes of illustration and not for purposes of limitation. The methods and compositions described herein can comprise any feature described herein either alone or in combination with any other feature(s) described herein. Changes and modifications may be made to the embodiments of the description. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

What is claimed is:

1. A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

2. The method of claim 1, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.

3. The method of claim 2, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 500 mg/day to about 1500 mg/day.

4. The method of claim 3, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.

5. The method of claim 1, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is administered in at least one dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, wherein the therapeutically effective amount of the prednisone is from about 0.01 mg/day to about 500 mg/day.

7. The method of claim 6, wherein the therapeutically effective amount of the prednisone is from about 10 mg/day to about 250 mg/day.

8. The method of claim 7, wherein the therapeutically effective amount of the prednisone is about 10 mg/day.

9. The method of claim 1, wherein the therapeutically effective amount of the prednisone is administered in at least one dosage form comprising about 5 mg of prednisone.

10. The method of claim 1, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

11. The method of claim 10, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

12. The method of claim 1, wherein said prostate cancer is refractory prostate cancer.

13. The method of claim 12, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.

14. The method of claim 13, wherein the at least one anti-cancer agent comprises a hormonal ablation agent, an anti-androgen agent, or an anti-neoplastic agent.

15. The method of claim 14, wherein the hormonal ablation agent comprises deslorelin, leuprolide, goserelin, or triptorelin.

16. The method of claim 14, wherein the anti-androgen agent comprises bicalutamide, flutamide, or nilutamide.

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17. The method of claim **14**, wherein the anti-neoplastic agent comprises docetaxel.

18. The method of claim **12**, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof 5 and about 0.01 mg/day to about 500 mg/day of prednisone.

19. The method of claim **18**, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone. 10

20. The method of claim **17**, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone. 15

* * * * *

EXHIBIT C

Docket No.: CGR5001USCNT1

I hereby certify that this correspondence is being transmitted via The Office Electronic Filing System (EFS) in accordance with 37 CFR 1.6(a)(4).

Date of Electronic (EFS) Transmission: June 4, 2013

Signature: /Laurie A. Phillips/ Name: Laurie A. Phillips

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Applicant(s):	Alan H. Auerbach	Conf. No.:	1597
Application No.:	13/034,340	Group Art:	1628
Filing Date:	February 24, 2011	Examiner:	San Ming R. Hui
Title:	Methods and Compositions for Treating Cancer		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE

Dear Sir:

In response to the final Office Action mailed March 4, 2013, Applicant submits the following amendments and remarks.

A list of the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Remarks

Claims 37-56 are pending.

Rejections Under 35 U.S.C. § 103

The rejection of claims 37-56 under 35 USC §103(a) as allegedly being unpatentable over O'Donell *et al.* (*British Journal of Cancer* 90:2317-2325 (2004)) ("O'Donell"), in view of Tannock *et al.* (*Journal of Clinical Oncology* 14:1756-1764 (1996)) (Tannock") was maintained. Applicant respectfully traverses this rejection.

In Applicant's previous reply, submitted January 11, 2013 (the "January Reply"), Applicant submitted the Ryan article. Ryan showed, *inter alia*, that the "median radiographic progression-free survival was 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone . . . Radiographic progression-free survival was positively correlated with overall survival." According to the Office, "the superior results of using abiraterone and prednisone together is expected because abiraterone and prednisone are known to be individually effective in treating prostate cancer. At least additive effective [sic] is expected." However, the Office failed to provide any reasoning to support the expectation of at least an additive effect. In fact, the Office's own cited art is in opposition to the Office's statement that at least an additive effect is expected.

Based on Tannock, the art cited by the Office, one of ordinary skill in the art would not expect at least an additive effect for overall survival of abiraterone and acetate and progesterone. Tannock teaches that "[t]here was no significant difference in overall survival [between prednisone alone and prednisone plus the anticancer agent mitoxantrone.]" One of ordinary skill in the art, reading Tannock, would expect there to be no difference in survival between one cancer agent alone, and that same cancer agent in combination with prednisone. Thus, the present invention possesses unexpected results and is non-obvious over the cited art.

Further, the present invention has displayed commercial success. Applicant submits herewith the currently United States Food & Drug Administration approved label

for ZYTIGATM (the “ZYTIGA label”). The ZYTIGA label indicates that “[abiraterone acetate] is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.” Taking ZYTIGA in accordance with the approved label represents a commercial embodiment of the presently claimed invention.

Applicant also submits herewith a news release from the U.S. Food and Drug Administration dated December 10, 2012 and titled “FDA expands Zytiga’s use for late-stage prostate cancer.” As can be seen from this 2012 news release, ZYTIGA was initially approved in April 2011 for use in patients whose prostate cancer progressed after treatment with docetaxel, a chemotherapy drug. ZYTIGA was further approved in December 2012 for use in prostate cancer patients prior to receiving chemotherapy.

Applicant also submits two further news releases from the U.S. Food and Drug Administration, one dated June 17, 2010, announcing approval of Jevtana for use in prostate cancer; and the other dated August 31, 2012, announcing the approval of Xtandi for use in patients whose prostate cancer progressed after treatment with docetaxel.

Applicant also submits herewith “Pharmaceuticals Commercial Overview”, a slideshow presented by Joaquin Duato on May 23, 2013 and currently available at http://files.shareholder.com/downloads/JNJ/2514173625x0x666408/bb2972ea-2099-4ab4-b2a3-afc39e710594/Pharmaceutical_Commercial_Overview_JNJ2013.pdf (the “2013 slideshow”). According to the 2013 slideshow, at slide 11, ZYTIGA is the most successful oral oncology launch in history.

The 2013 slideshow, at slide 12, further shows the July 2012 to April 2013 ZYTIGA market share of chemo refractory prostate cancer patients, i.e., patients who have previously received chemotherapy treatment and the December 2012 to April 2013 market share of chemo naïve prostate cancer patients, i.e., patients who have not previously received chemotherapy treatment. As can be seen from the figure on the left of slide 12, ZYTIGA had almost 70% market share in July of 2012 for chemo refractory prostate cancer patients, just slightly over a year after ZYTIGA’s initial approval, and despite the fact that a JEVTANA had been approved two years earlier. Despite another product, XTANDI, being introduced in August of 2012, by April of 2013, ZYTIGA was

still the market leader as of April 2013 with 57% market share in chemo refractory prostate cancer patients.

As can be seen from the figure on the right of slide 12, shortly after its approval for chemo-naïve patients in December 2012, ZYTIGA had a market share of 15%. As of April 2013, ZYTIGA's market share was 20%, higher than two other available therapies, docetaxel and XTANDI, and approaching the market share of bicalutamide, a drug first approved in 2001 for prostate cancer.

Thus, not only is ZYTIGA the most successful oral oncology launch in history, two years after its initial approval it is still the market leader for chemo refractory patients despite an earlier-introduced therapy and a later-introduced therapy. ZYTIGA also holds a strong market share in the chemo naïve prostate cancer population, despite the presence of other marketed products. This commercial success demonstrates the non-obviousness of the presently claimed invention.

Even assuming, *arguendo*, the cited art suggests the claimed combination, the present invention has shown surprising results, and commercial success. Thus, the claims are non-obvious over the cited art. Accordingly, Applicant requests reconsideration and withdrawal of the rejection under 35 USC §103(a).

Docket No.: CGR5001USCNT1

III. CONCLUSION

Early consideration and prompt allowance of the claims are respectfully requested. Should the office require anything further, it is invited to contact Applicant's representative at the telephone number below.

Applicant respectfully requests that a timely Notice of Allowance be issued in the present application. Should the office require anything further, it is invited to contact Applicant's representative at the telephone number below.

Respectfully submitted,

JOHNSON & JOHNSON
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-3957
Dated: June 4, 2013
Customer No.: 27777

By: /Andrea Jo Kamage/
Andrea Jo Kamage
Reg. No. 43,703

I hereby certify that this correspondence is being transmitted via The Office Electronic Filing System (EFS) in accordance with 37 CFR 1.6(a)(4).

Date of Electronic (EFS) Transmission: June 4, 2013

Signature: /Laurie A. Phillips/ Name: Laurie A. Phillips

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Applicant(s):	Alan H. Auerbach	Conf. No.:	1597
Application No.:	13/034,340	Group Art:	1628
Filing Date:	February 24, 2011	Examiner:	San Ming R. Hui
Title:	Methods and Compositions for Treating Cancer		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL

Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision of the Examiner dated March 4, 2013 finally rejecting Claims 37-56 of the above-identified application.

The item(s) checked below are appropriate:

1. ☐ An extension of time to respond to the final rejection was granted on _____ for month(s).
2. ☐ A Petition For Extension Of Time under 37 CFR 1.136 is attached hereto in triplicate.
3. ☒ A timely response to the final rejection has been filed.
4. ☒ Fee \$500.00: for filing of Notice of Appeal
☐ Not required (fee paid in prior appeal)
☒ Charge to Deposit Account No. 10-0750/AJK/CGR5001.
☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment in connection herewith to Deposit Account No. 10-0750/AJK/CGR5001.

Respectfully submitted,

JOHNSON & JOHNSON
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-3957
Dated: June 4, 2013
Customer No.: 27777

By: /Andrea Jo Kamage/
Andrea Jo Kamage
Reg. No. 43,703



U.S. Food and Drug Administration

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FDANEWS RELEASE

For Immediate Release: Aug. 31, 2012

Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

FDA approves new treatment for a type of late stage prostate cancer

The U.S. Food and Drug Administration today approved Xtandi (enzalutamide) to treat men with late-stage (metastatic) castration-resistant prostate cancer that has spread or recurred, even with medical or surgical therapy to minimize testosterone.

Approved for prostate cancer patients previously treated with docetaxel, another anti-cancer treatment, Xtandi was reviewed under the FDA's priority review program. The program provides for an expedited six-month review for drugs that may offer major advances in treatment or that provide a treatment when no adequate therapy exists. Xtandi received FDA approval three months ahead of the product's prescription drug user fee goal date of Nov. 22, 2012.

"The need for additional treatment options for advanced prostate cancer continues to be important for patients," said Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research. "Xtandi is the latest treatment for this disease to demonstrate its ability to extend a patient's life."

Prostate cancer forms in a gland in the male reproductive system found below the bladder and in front of the rectum. The male sex hormone testosterone stimulates the prostate tumors to grow. According to the National Cancer Institute, an estimated 241,740 men will be diagnosed with prostate cancer and 28,170 will die from the disease in 2012.

The safety and effectiveness of Xtandi was evaluated in a study of 1,199 patients with metastatic castration-resistant prostate cancer who had received prior treatment with docetaxel. The study was designed to measure overall survival (the length of time before death) in men receiving Xtandi compared with men receiving a placebo (sugar pill). The median overall survival for patients receiving Xtandi was 18.4 months, compared with 13.6 months for the patients who received placebo.

The most common side effects observed in study participants taking Xtandi were weakness or fatigue, back pain, diarrhea, joint pain, hot flush, tissue swelling, musculoskeletal pain, headache, upper respiratory infections, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, difficulty sleeping, lower respiratory infections, blood in urine, tingling sensation, anxiety, and high blood pressure.

Seizures occurred in approximately 1 percent of those receiving Xtandi. Patients in the study who had a seizure stopped Xtandi therapy. The clinical study excluded patients with a history of seizure, an underlying brain injury with loss of consciousness, a temporary decrease in blood to the brain within the past 12 months, a stroke, brain metastases, an abnormal connection of the arteries and veins in the brain, or patients taking medications that may lower the seizure threshold. The safety of Xtandi is unknown in patients with these conditions.

Xtandi will be co-marketed by Astellas Pharma U.S., Inc. of Northbrook, IL and Medivation, Inc. of San Francisco, CA.

For more information:

FDA: Office of Hematology and Oncology Products¹

FDA: Approved Drugs: Questions and Answers²

FDA: Drug Innovation³

FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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FDANEWS RELEASE

For Immediate Release: June 17, 2010

Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

FDA Approves New Treatment for Advanced Prostate Cancer

The U.S. Food and Drug Administration today approved Jevtana (cabazitaxel), a chemotherapy drug used in combination with the steroid prednisone to treat men with prostate cancer. Jevtana is the first treatment for advanced, hormone-refractory, prostate cancer that has worsened during or after treatment with docetaxel, a commonly used drug for advanced prostate cancer.

In prostate cancer, the male sex hormone testosterone can cause prostate tumors to grow. Drugs, surgery or other hormones are used to reduce testosterone production or to block it. Some men have hormone refractory prostate cancer, meaning the prostate cancer cells continue to grow, despite testosterone suppression. Different treatments are needed for men with this type of cancer.

Jevtana was reviewed under the FDA's priority review program, which provides for an expedited six-month review for drugs that may offer major advances in treatment, or provide a treatment when no adequate therapy exists. Jevtana received approval ahead of the product's Sept. 30, 2010, goal date.

"Patients have few therapeutic options in this disease setting," said Richard Pazdur, M.D., director of the Office of Oncology Drug Products, part of the FDA's Center for Drug Evaluation and Research. "FDA was able to review and approve the application for Jevtana in 11 weeks, expediting the availability of this drug to men with prostate cancer."

Jevtana's safety and effectiveness was established in a single, 755-patient study. All study participants had previously received docetaxel. The study was designed to measure overall survival (the length of time before death) in men who received Jevtana in combination with prednisone compared with those who received the chemotherapy drug, mitoxantrone, in combination with prednisone. The median overall survival for patients receiving the Jevtana regimen was 15.1 months compared with 12.7 months for those who received the mitoxantrone regimen.

Side effects in those treated with Jevtana included decrease in infection-fighting white blood cells (neutropenia), anemia, decrease in the number of white blood cells (leukopenia), low level of platelets in the blood (thrombocytopenia), diarrhea, fatigue, nausea, vomiting, constipation, weakness (asthenia), and renal failure.

Prostate cancer, which usually occurs in older men, is the second most common cancer among men in the United States, behind skin cancer. In 2006, the most recent year for which numbers were available, 203,415 men developed prostate cancer and 28,372 men died from the disease, according to the Centers for Disease Control and Prevention.

Jevtana is marketed by Bridgewater, N.J.-based Sanofi-Aventis.

For more information:

- FDA: Office of Oncology Drug Products¹
- CDC: Informed Decision Making About Prostate Cancer²
- NCI: Prostate Cancer³

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FDANEWS RELEASE

For Immediate Release: Dec. 10, 2012

Media Inquiries: Stephanie Yao, 301-796-0394, stephanie.yao@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

FDA expands Zytiga's use for late-stage prostate cancer

Drug can now be used before treatment with chemotherapy

The U.S. Food and Drug Administration today expanded the approved use of Zytiga (abiraterone acetate) to treat men with late-stage (metastatic) castration-resistant prostate cancer prior to receiving chemotherapy.

The FDA initially approved Zytiga in April 2011 for use in patients whose prostate cancer progressed after treatment with docetaxel, a chemotherapy drug. Zytiga is a pill that decreases the production of male sex hormone testosterone.

In prostate cancer, testosterone stimulates prostate tumors to grow. Drugs or surgery are used to reduce testosterone production or to block testosterone's effects. Some men have castration-resistant prostate cancer, meaning the prostate cancer cells continue to grow even with low levels of testosterone.

"Today's approval demonstrates the benefit of further evaluating a drug in an earlier disease setting and provides patients and health care providers the option of using Zytiga earlier in the course of treatment," said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

The FDA reviewed Zytiga's application for this new indication under the agency's priority review program. The program provides for an expedited six-month review for drugs that may offer major advances in treatment or provide a treatment when no adequate therapy exists.

Zytiga's safety and effectiveness for its expanded use were established in a clinical study of 1,088 men with late-stage, castration-resistant prostate cancer who had not previously received chemotherapy. Participants received either Zytiga or a placebo (sugar pill) in combination with prednisone.

The study was designed to measure the length of time a patient lived before death (overall survival) and the length of time a patient lived without further tumor growth as assessed by imaging studies (radiographi progression-free survival, or rPFS).

Patients who received Zytiga had a median overall survival of 35.3 months compared with 30.1 months for those receiving the placebo. Study results also showed Zytiga improved rPFS. The median rPFS was 8.3 months in the placebo group and had not yet been reached for patients treated with Zytiga at the time of analysis.

The most common side effects reported in those receiving Zytiga include fatigue, joint swelling or discomfort, swelling caused by fluid retention, hot flush, diarrhea, vomiting, cough, high blood pressure, shortness of breath, urinary tract infection, and bruising.

The most common laboratory abnormalities included low red blood cell count; high levels of the enzyme alkaline phosphatase, which can be a sign of other serious medical problems; high levels of fatty acids, sugar, and liver enzymes in the blood; and low levels of lymphocytes, phosphorous and potassium in the blood.

Zytiga is marketed by Horsham, Pa.-based Janssen Biotech Inc.

For more information:

FDA approves Zytiga for late-stage prostate cancer (April 2011)¹

FDA: Office of Hematology and Oncology Products²

FDA: Approved Drugs: Questions and Answers³

NCI: Prostate Cancer⁴

This press release was updated on Dec. 10, 2012 at 2:30 p.m. to correct the date when Zytiga was

originally approved to April 2011.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA®

(abiraterone acetate) Tablets

For Oral Administration

Initial U.S. Approval – 2011

RECENT MAJOR CHANGES

Indications and usage (1)	12/2012
Contraindications, Pregnancy (4.1)	12/2012
Warnings and Precautions, Mineralocorticoid excess (5.1)	12/2012
Warnings and Precautions, Adrenocortical Insufficiency (5.2)	12/2012
Warnings and Precautions, Hepatotoxicity (5.3)	12/2012

INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. (1)

DOSAGE AND ADMINISTRATION

Recommended dose: ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water. Do not crush or chew tablets. (2.1)

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.2)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablet 250 mg (3)

CONTRAINDICATIONS

- ZYTIGA is contraindicated in women who are or may become pregnant. (4.1, 8.1)

ZYTIGA® (abiraterone acetate) Tablets**WARNINGS AND PRECAUTIONS**

- Mineralocorticoid excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure in Study 1 or LVEF < 50% or NYHA Class II to IV heart failure in Study 2 was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)
- Food effect: ZYTIGA must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (≥ 10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and confusion.

The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7)

USE IN SPECIFIC POPULATIONS

- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for Patient Counseling Information and FDA-approved patient labeling.

Revised: [12/2012]

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ZYTIGA® (abiraterone acetate) Tablets**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dosage**

The recommended dose of ZYTIGA is 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken [see *Clinical Pharmacology* (12.3)]. The tablets should be swallowed whole with water. Do not crush or chew tablets.

2.2 Dose Modification Guidelines**Hepatic Impairment**

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

Avoid ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA [see *Warnings and Precautions* (5.3)]. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

3 DOSAGE FORMS AND STRENGTHS

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side.

4 CONTRAINDICATIONS**4.1 Pregnancy**

ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss [see *Use in Specific Populations* (8.1)].

5 WARNINGS AND PRECAUTIONS**5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess**

ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see *Clinical Pharmacology* (12.1)]. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA [see *Adverse Reactions* (6)].

Co-administration of a corticosteroid suppresses adrenocorticotrophic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular

ZYTIGA® (abiraterone acetate) Tablets

ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials [see *Clinical Studies* (14)]. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

5.2 Adrenocortical Insufficiency

Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations [see *Warnings and Precautions* (5.1)].

5.3 Hepatotoxicity

In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN [see *Dosage and Administration* (2.2)].

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

5.4 Increased ZYTIGA Exposures with Food

ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3)].

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess [see *Warnings and Precautions* (5.1)]
- Adrenocortical Insufficiency [see *Warnings and Precautions* (5.2)]
- Hepatotoxicity [see *Warnings and Precautions* (5.3)]
- Increased ZYTIGA Exposures with Food [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

ZYTIGA® (abiraterone acetate) Tablets

The most common adverse drug reactions ($\geq 10\%$) reported in the two randomized clinical trials that occurred more commonly ($>2\%$) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and confusion.

The most common laboratory abnormalities ($>20\%$) reported in the two randomized clinical trials that occurred more commonly ($\geq 2\%$) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy

Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT $\geq 2.5\times$ ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT $> 5\times$ ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a $\geq 2\%$ absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
	All Grades ¹ %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort ²	29.5	4.2	23.4	4.1
Muscle discomfort ³	26.2	3.0	23.1	2.3
General disorders				
Edema ⁴	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures ⁵	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia ⁶	7.2	1.1	4.6	1.0
Chest pain or chest discomfort ⁷	3.8	0.5	2.8	0
Cardiac failure ⁸	2.3	1.9	1.0	0.3

¹Adverse events graded according to CTCAE version 3.0

²Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

³Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness

⁴Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

⁵Includes all fractures with the exception of pathological fracture

⁶Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia

⁷Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively)

⁸Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

ZYTIGA® (abiraterone acetate) Tablets

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

Laboratory Abnormality	Abiraterone (N=791)		Placebo (N=394)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Study 2: Metastatic CRPC Prior to Chemotherapy

Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT $\geq 2.5\times$ ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a $\geq 2\%$ absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in $\geq 2\%$ of Patients on the ZYTIGA Arm in Study 2

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
	All Grades ¹ %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema ²	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort ³	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

¹Adverse events graded according to CTCAE version 3.0

²Includes terms Edema peripheral, Pitting edema, and Generalized edema

³Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently ($>5\%$) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

ZYTIGA® (abiraterone acetate) Tablets**Table 4: Laboratory Abnormalities in > 15% of Patients in the ZYTIGA Arm of Study 2**

Laboratory Abnormality	Abiraterone (N = 542)		Placebo (N = 540)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia ¹	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypertension	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

¹Based on non-fasting blood draws**Cardiovascular Adverse Reactions:**

In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

7 DRUG INTERACTIONS**7.1 Effects of Abiraterone on Drug Metabolizing Enzymes**

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug [see *Clinical Pharmacology* (12.3)].

In vitro, ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

7.2 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Pregnancy Category X [see Contraindications (4.1)].**

ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥ 10 mg/kg/day, decreased fetal ano-genital distance at ≥ 30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥ 10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

ZYTIGA® (abiraterone acetate) Tablets**8.3 Nursing Mothers**

ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild ($n = 8$) or moderate ($n = 8$) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST $> 5 \times$ ULN or total bilirubin $> 3 \times$ ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3)].

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.3), and *Clinical Pharmacology* (12.3)].

8.7 Patients with Renal Impairment

In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function ($N=8$) and those with end stage renal disease (ESRD) on hemodialysis ($N=8$) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3)].

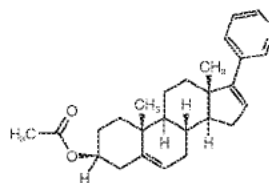
10 OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

11 DESCRIPTION

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17 α -hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3 β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{32}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

ZYTIGA® (abiraterone acetate) Tablets**12 CLINICAL PHARMACOLOGY****12.1 Mechanism of Action**

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α -hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17 α -hydroxy derivatives by 17 α -hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals [see *Warnings and Precautions* (5.1)].

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

12.3 Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean \pm SD) of C_{max} were 226 \pm 178 ng/mL and of AUC were 1173 \pm 690 ng·hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and AUC_{0- ∞} were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water [see *Dosage and Administration* (2.1)].

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean \pm SD) is 19,669 \pm 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

Following oral administration of ¹⁴C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean \pm SD) is 12 \pm 5 hours. Following oral administration of ¹⁴C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

ZYTIGA® (abiraterone acetate) Tablets**Patients with Hepatic Impairment**

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. ZYTIGA has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.6)].

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function [see *Use in Specific Populations* (8.7)].

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8, a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextromethorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold [see *Drug Interactions* (7.1)].

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution [see *Drug Interactions* (7.2)].

12.6 QT Prolongation

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received ZYTIGA orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

13 NONCLINICAL TOXICOLOGY**13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

ZYTIGA has the potential to impair reproductive function and fertility in humans based on findings in animals. In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at \geq 50 mg/kg/day in rats and \geq 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone [see *Nonclinical Toxicology* (13.2)]. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

In fertility studies in rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in males dosed for 4 weeks at \geq 30 mg/kg/day. Mating of untreated females with males that received 30 mg/kg/day abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration. Female rats dosed for 2 weeks until day 7 of pregnancy at \geq 30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on female rats were reversible after 4 weeks from the last abiraterone acetate administration. The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1000 mg/day based on body surface area.

ZYTIGA® (abiraterone acetate) Tablets**13.2 Animal Toxicology and/or Pharmacology**

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at ≥ 50 mg/kg/day (similar to the human clinical exposure based on AUC). In the 39-week monkey study, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA in patients with metastatic castration-resistant prostate cancer (CRPC) that has progressed on androgen deprivation therapy was demonstrated in two randomized, placebo-controlled, multicenter phase 3 clinical trials. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from these trials.

Study 1

Patients with metastatic CRPC who had received prior docetaxel chemotherapy: A total of 1195 patients were randomized 2:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory-Short Form score of ≥ 4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival in patients treated with ZYTIGA compared to patients in the placebo arm (Table 5 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 5).

Table 5: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 1 (Intent-to-Treat Analysis)

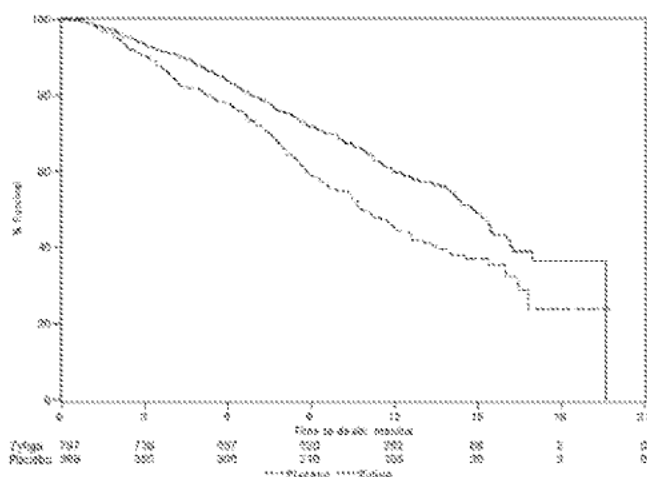
	ZYTIGA (N=797)	Placebo (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p-value ^a	< 0.0001	
Hazard ratio (95% CI) ^b	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) ^b	0.740 (0.638, 0.859)	

^a P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).

^b Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

ZYTIGA® (abiraterone acetate) Tablets

Figure 1: Kaplan-Meier Overall Survival Curves in Study 1 (Intent-to-Treat Analysis)

**Study 2**

Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy

In Study 2, 1088 patients were randomized 1:1 to receive either ZYTIGA at a dose of 1,000 mg once daily (N=546) or Placebo once daily (N=542). Both arms were given concomitant prednisone 5 mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with ZYTIGA was 95.4% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

Radiographic progression-free survival was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prestate Cancer Working Group 2 criteria) and/or modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

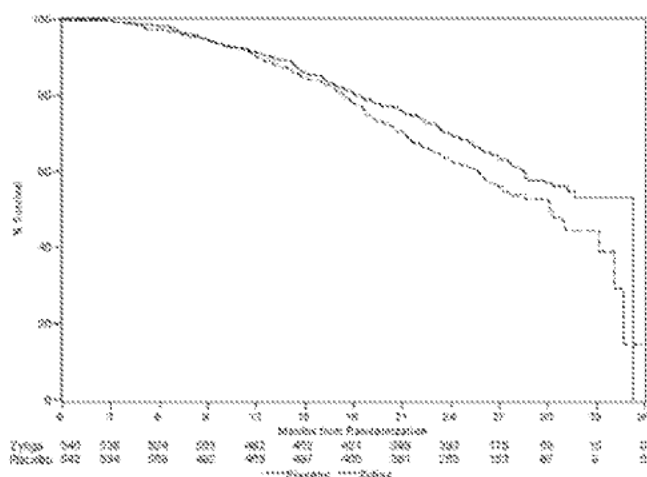
At the protocol pre-specified third interim analysis for overall survival, 37% (200 of 546) of patients treated with ZYTIGA, compared with 43% (234 of 542) of patients treated with placebo, had died. Overall survival was longer for ZYTIGA than placebo with a hazard ratio of 0.792 (95% CI: 0.655 - 0.956). The p-value was 0.0151 which did not meet the pre-specified value for statistical significance (Table 6 and Figure 2).

Table 6: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

Overall Survival	ZYTIGA (N=546)	Placebo (N=542)
Deaths	200 (37%)	234 (43%)
Median survival (months) (95% CI)	35.3 (31.24, 35.29)	30.1 (27.30, 34.10)
p-value ^a	0.0151	
Hazard ratio ^b (95% CI)	0.792 (0.655, 0.956)	

^a P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

^b Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

ZYTIGA® (abiraterone acetate) Tablets**Figure 2: Kaplan Meier Overall Survival Curves in Study 2 (Intent-to-Treat analysis)**

At the pre-specified rPFS analysis, 150 (28%) patients treated with ZYTIGA and 251 (46%) patients treated with placebo had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 7 and Figure 3).

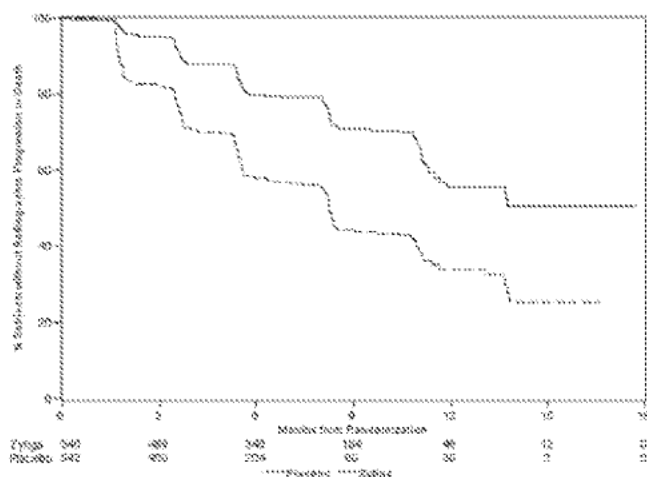
Table 7: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

Radiographic Progression-free Survival	ZYTIGA (N=546)	Placebo (N=542)
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value ^a	<0.0001	
Hazard ratio ^b (95% CI)	0.425 (0.347, 0.522)	

NR= Not reached

^a P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

^b Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

Figure 3: Kaplan Meier Curves of Radiographic Progression-free Survival in Study 2 (Intent-to-Treat Analysis)

The primary efficacy analyses are supported by the following prospectively defined endpoints. The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving ZYTIGA and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487, 0.691], p<0.0001).

ZYTIGA® (abiraterone acetate) Tablets

The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686, 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves [see Use in Specific Populations (8.1)].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Manufactured by:

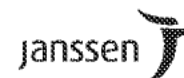
Patheon Inc.
Mississauga, Canada

Manufactured for:

Janssen Biotech, Inc.
Horsham, PA 19044

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Revised: December 2012



ZYTIGA® (abiraterone acetate) Tablets

PATIENT INFORMATION
ZYTIGA® (Zye-tee-ga)
(abiraterone acetate)
Tablets

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

Who should not take ZYTIGA?

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?
Before you take ZYTIGA, tell your healthcare provider if you:

- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See "Who should not take ZYTIGA?"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "Who should not take ZYTIGA?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA one time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.

ZYTIGA® (abiraterone acetate) Tablets

- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?**ZYTIGA may cause serious side effects including:**

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema).** Tell your healthcare provider if you get any of the following symptoms:
 - o dizziness
 - o fast heartbeats
 - o feel faint or lightheaded
 - o headache
 - o confusion
 - o muscle weakness
 - o pain in your legs
 - o swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

The most common side effects of ZYTIGA include:

- o weakness
- o joint swelling or pain
- o swelling in your legs or feet
- o hot flashes
- o diarrhea
- o vomiting
- o cough
- o high blood pressure
- o shortness of breath
- o urinary tract infection
- o bruising
- o low red blood cells (anemia) and low blood potassium levels
- o high blood sugar levels, high blood cholesterol and triglycerides
- o certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?

- Store ZYTIGA at 59°F to 86°F (15°C to 30°C).

Keep ZYTIGA and all medicines out of the reach of children.

ZYTIGA® (abiraterone acetate) Tablets

General information about ZYTIGA.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give your ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for healthcare professionals.

For more information contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or www.Zytiga.com.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, micro-crystalline cellulose, povidone, and sodium lauryl sulfate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Patheon Inc.
Mississauga, Canada

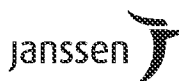
Manufactured for:

Janssen Biotech, Inc.
Horsham, PA 19044

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Revised: December 2012

2000005445

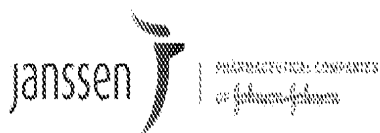
K08Z121174



Pharmaceuticals Commercial Overview

Joaquin Duato

Worldwide Chairman, Pharmaceuticals



Excellence in Execution

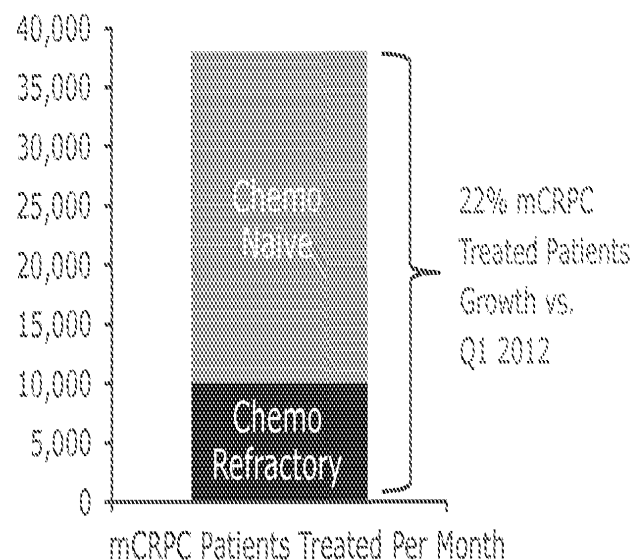
ZYTIGA®: Most Successful Oral Oncology Launch in History¹



- Generated \$961MM revenue in 2012
- Changed treatment paradigm for metastatic Castration-Resistant Prostate Cancer (mCRPC)
- Approved in 75+ countries for chemo refractory and more than 60,000 patients treated
- Approved in 40+ countries for chemo naïve (US/EU approvals December 2012)

WW Market ²		
2012	2017	CAGR
\$4.5B	\$8.0B	12%

Q1 2013 SALES	Q1 YoY GROWTH [*]
\$344MM	72%

Q1 2013 US Patient Population³

Sources: 1. EvaluatePharma, Oncology launch view orals, May 14, 2013. 2. EvaluatePharma, April 2013 (Prostate Cancer market). 3. IMS Health and internal analysis.

* Operational change.

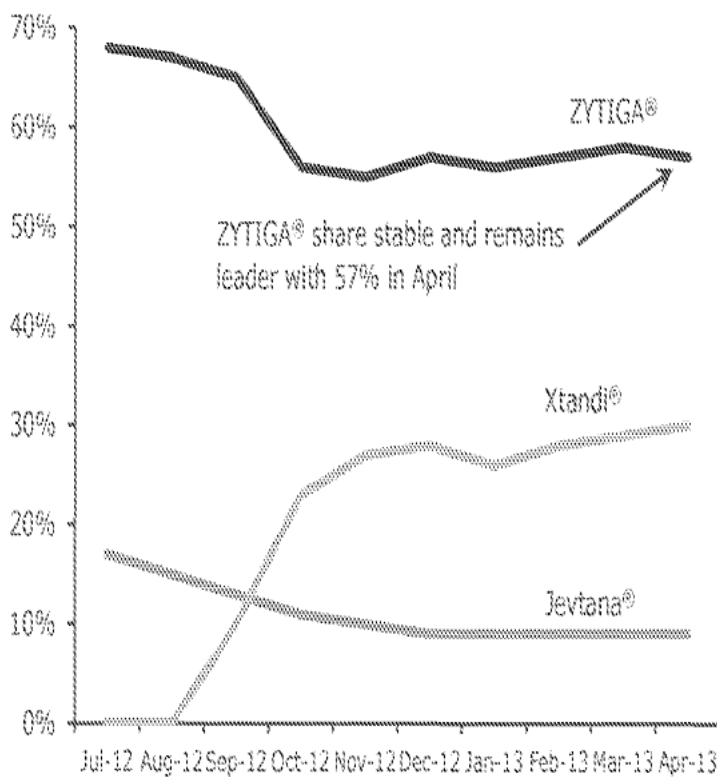
Excellence in Execution

Overall US Patient Share Continues to Grow

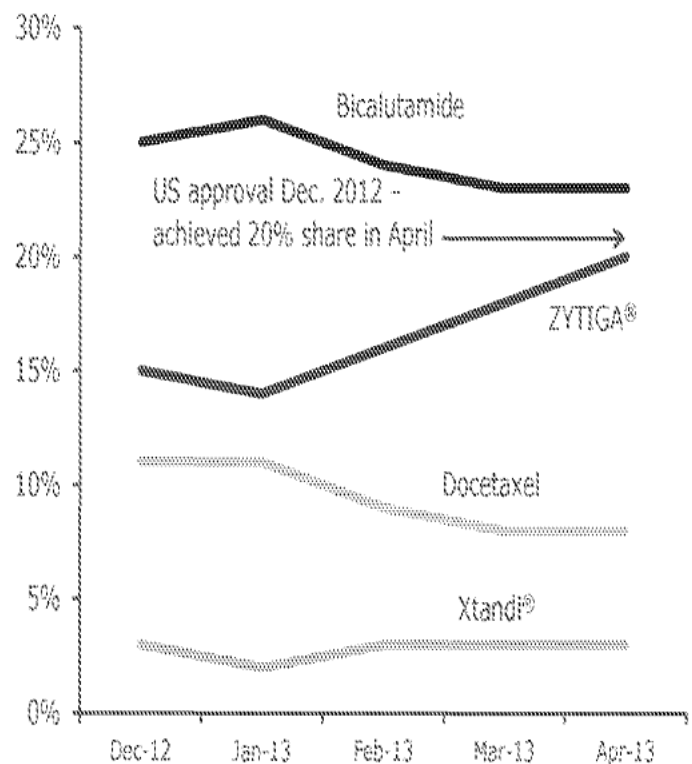
Total mCRPC Share in April Over 30%, Up ~3 Points from Q4 2012



Chemo Refractory



Chemo Naïve



Sources: ZYTIGA® - IMS DDD, Wolters Kluwer Health (WKH). Xtandi® - WKH data based on ZYTIGA® Xponent samples to IMS DDD universe (sample of claims from SPP/Pharmacy to Payer). Note: Patient share percentages are preliminary estimates based on limited data available. Patient level detailed sales data by indication only available on a 2 month lag (i.e., March data at the beginning of June).

Electronic Patent Application Fee Transmittal

Application Number:	13034340			
Filing Date:	24-Feb-2011			
Title of Invention:	Methods and Compositions for Treating Cancer			
First Named Inventor/Applicant Name:	Alan H. Auerbach			
Filer:	Andrea J. Kamage/Laurie Phillips			
Attorney Docket Number:	CGR5001USCNT1			
Filed as Large Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				800

Electronic Acknowledgement Receipt

EFS ID:	15948999
Application Number:	13034340
International Application Number:	
Confirmation Number:	1597
Title of Invention:	Methods and Compositions for Treating Cancer
First Named Inventor/Applicant Name:	Alan H. Auerbach
Customer Number:	27777
Filer:	Andrea J. Kamage/Laurie Phillips
Filer Authorized By:	Andrea J. Kamage
Attorney Docket Number:	CGR5001USCNT1
Receipt Date:	04-JUN-2013
Filing Date:	24-FEB-2011
Time Stamp:	18:03:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$800
RAM confirmation Number	5706
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment After Final	CGR5001USCNT1_Response_to_OA_June_2013.pdf	116303 8487a35b7f7f2ebe2257327facdadeef903e431d	no	9
Warnings:					
Information:					
2	Notice of Appeal Filed	CGR5001USCNT1_Notice_of_Appeal_June_2013.pdf	74179 d713f789b27c0940884a4b38d7f4be85e387e2c2	no	1
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	Press_Announcements_FDA_approves_new_treatment_for_a_type_of_late_stage_prostate_cancer_Xtandi.pdf	113364 5d03a7faa234e138ade991ee13c93c818c562ddf	no	2
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	Press_Announcements_FDA Approves New Treatment for Advanced Prostate Cancer Jevtana.pdf	112420 d4c1093684962c8452ccdac5817863c1297517af	no	2
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	Press_Announcements_FDA expands_Zytigas_use_for_late_stage_prostate_cancer.pdf	132426 4c05fb496c3354026ade31614d9a0c0b679caafe	no	2
Warnings:					
Information:					
6	Miscellaneous Incoming Letter	ZYTIGA_full_product_information.pdf	223379 1c1f484d8b4c97a61baa8a7b81cb389da62f91c7	no	9
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	Pharmaceutical_Commercial_Opportunity_Interview_JNJ2013.pdf	1283733 4329919cff3db5a30d535af59b22f6f012fd465d	no	41
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30009 014857821ac9105732a8e7a473cfb18c9547e12f	no	2

Warnings:**Information:****Total Files Size (in bytes):**

2085813

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 13/034,340		Filing Date 02/24/2011		<input type="checkbox"/> To be Mailed		
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO										
APPLICATION AS FILED – PART I										
(Column 1)		(Column 2)								
FOR	NUMBER FILED	NUMBER EXTRA			RATE (\$)	FEE (\$)				
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A			N/A					
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A			N/A					
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A			N/A					
TOTAL CLAIMS (37 CFR 1.16(j))	minus 20 =	*			X \$ =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*			X \$ =					
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).									
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL					
APPLICATION AS AMENDED – PART II										
(Column 1)		(Column 2)		(Column 3)						
AMENDMENT	06/04/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 20	Minus	** 36	= 0	X \$80 =		0		
	Independent (37 CFR 1.16(h))	* 1	Minus	***4	= 0	X \$420 =		0		
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))									
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
					TOTAL ADD'L FEE		0			
(Column 1)		(Column 2)		(Column 3)						
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =				
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =				
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))									
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
					TOTAL ADD'L FEE					
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>										

LIE
/BRIDGET MONROE/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

EXHIBIT D

In the United States Patent and Trademark Office

Before the Patent Trial and Appeal Board

AMERIGEN PHARMACEUTICALS LIMITED,

Petitioner

v.

JANSSEN ONCOLOGY, INC.,

Patent Owner

U.S. Patent No. 8,822,438 to Auerbach *et al.*

Issue Date: September 2, 2014

Title: Methods and Compositions for Treating Cancer

Inter Partes Review No. Unassigned

Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438 Under
35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-42.80, 42.100-42.123

Mail Stop “PATENT BOARD”

Patent Trial and Appeal Board

U.S. Patent and Trademark Office

P.O. Box 1450

Alexandria, Virginia 22313–1450

Submitted Electronically via the Patent Review Processing System

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**LISTING OF EXHIBITS PURSUANT TO 37 C.F.R. § 42.63(e) AND
TABLE OF ABBREVIATIONS**

Exhibit	Description
AMG 1001	U.S. Patent No. 8,822,438, Auerbach and Belldegrum, “Methods and Compositions for Treating Cancer” (“the ‘438 patent”)
AMG 1002	Declaration of Dr. Scott Serels, MD (“Serels Decl.”)
AMG 1003	O’Donnell, A. <i>et al.</i> , “Hormonal impact of the 17 α -hydroxylase/C ₁₇ -20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer,” <i>British Journal of Cancer</i> , (90):2317-2325 (2004) (“O’Donnell”)
AMG 1004	Gerber, G.S. <i>et al.</i> , “Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic cancer,” <i>The Journal of Urology</i> , 144(5):1177-9 (1990) (“Gerber”)
AMG 1005	U.S. Patent No. 5,604,213, Barrie S.E. <i>et al.</i> , “17-Substituted Steroids Useful In Cancer Treatment” (“the ‘213 patent”)
AMG 1006	Tannock <i>et al.</i> , “Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points,” <i>The Journal of Clinical Oncology</i> , 14:1756-1764 (1996) (“Tannock”)
AMG 1007	February 3, 2012 Office Action (excerpt from prosecution history of ‘438 patent)
AMG 1008	July 3, 2012 Response (excerpt from prosecution history of ‘438 patent)

AMG 1009	Ryan <i>et al.</i> , “Abiraterone in metastatic prostate cancer without previous chemotherapy,” <i>The New England Journal of Medicine</i> , 368:138-148 (2012).
AMG 1010	January 11, 2013 Response (excerpt from prosecution history of '438 patent)
AMG 1011	March 4, 2013 Office Action (excerpt from prosecution history of '438 patent)
AMG 1012	June 4, 2013 Response (excerpt from prosecution history of '438 patent)
AMG 1013	July 3, 2013 Notice of Allowance (excerpt from prosecution history of '438 patent)
AMG 1014	October 25, 2013 Notice of Allowance (excerpt from prosecution history of '438 patent)
AMG 1015	February 11, 2014 Notice of Allowance (excerpt from prosecution history of '438 patent)
AMG 1016	June 2, 2014 Notice of Allowance (excerpt from prosecution history of '438 patent)
AMG 1017	Declaration of Dr. DeForest McDuff, PhD (“McDuff Declaration”)
AMG 1018	2011 Zytiga® Approval Prescribing Information
AMG 1019	2015 Zytiga® Prescribing Information, Co-administration Brochure
AMG 1020	Harris <i>et al.</i> , “Low dose Ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer,” <i>The Journal of Urology</i> , volume 168:542-545 (August 2002)
AMG 1021	William Oh, “Secondary hormonal therapies in the treatment of prostate cancer,” <i>Urology</i> , volume 60:87-93 (Supplement 3A) (September 2002)

AMG 1022	Tannock, I. <i>et al.</i> , “Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer,” <i>N. Eng. J. Med.</i> , 351:1502-12 (2004)
AMG 1023	Attard, G. <i>et al.</i> , “Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer,” <i>Br. J. Urol.</i> 96(9): 1241-1246 (2005)
AMG 1024	Hellerstedt <i>et al.</i> , “The Current State of Hormonal Therapy for Prostate Cancer,” <i>CA Cancer J. Clin.</i> , 52:154-179 (2002).
AMG 1025	Kasper, D.L. <i>et al.</i> (Eds.), <i>Harrison's Principles of Internal Medicine</i> , 16 th Edition (2005), p. 549.
AMG 1026	Auchus, R.J. “The genetics, pathophysiology, and management of human deficiencies of P450c17,” <i>Endocrinol. Metab. Clin. North Am.</i> (30)1:101-119 (2001)
AMG 1027	Costa-Santos, M. <i>et al.</i> , “Two Prevalent CYP17 Mutations and Genotype-Phenotype Correlations in 24 Brazilian Patients with 17-Hydroxylase Deficiency,” <i>J. Clin. Endocrin. & Metabol.</i> (89)1:49-
AMG 1028	Jubelirer, S.J., <i>et al.</i> , “High dose ketoconazole for the treatment of hormone refractory metastatic prostate carcinoma,” <i>J. Urol.</i> , 142(1):89-901 (1989)
AMG 1029	U.S. Patent 5,688,977, Sisti, N.J. <i>et al.</i> , “Method for Docetaxel Synthesis”
AMG 1030	U.S. Food and Drug Administration ("FDA") FDA News Release dated May 19, 2004, “FDA Approves New Indication for Taxotere-Prostate Cancer”

AMG 1031	Tannock, I. <i>et al.</i> , “Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response,” <i>Journal of Clin. Oncology</i> , 7:590-7 (1989)
AMG 1032	Taxotere® Prescribing Information (2004)
AMG 1033	Scher, H.I. <i>et al.</i> , “Increased survival with Enzalutamide in Prostate Cancer after Chemotherapy,” <i>New Eng. J. Med.</i> , 367:1187-97 (2012)
AMG 1034	de Bono, J.S. <i>et al.</i> , “Abiraterone and Increased Survival in Metastatic Prostate Cancer,” <i>New Engl. J. Med.</i> , 364:1995-2005 (2011)
AMG 1035	Orange Book listing for Zytiga®
AMG 1036	Initial Application (excerpt from prosecution history of ’438 patent)
AMG 1037	November 25, 2011 Office Action (excerpt from prosecution history of ’438 patent)
AMG 1038	December 21, 2011 Response (excerpt from prosecution history of ’438 patent)
AMG 1039	September 11, 2012 Office Action (excerpt from prosecution history of ’438 patent)
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AMG 1043	Cowen & Company, “Quick Take – Johnson & Johnson,”
AMG 1044	Credit Suisse, “Prostate Cancer – Implications of Zytiga’s Pre-Chemo Approval,” 12/11/2012.
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AMG 1063	William Blair, “Medivation, Inc. – Looking into Recent Weaknesses,” 7/15/2015.
AMG 1064	Zytiga Brochure, Putting Prednisone in Perspective, 3/2015.
AMG 1065	Zytiga Label, 5/20/2015.
AMG 1066	Zytiga Website, How Zytiga® (abiraterone acetate) Works, https://www.zytiga.com/print/about-zytiga/how-zytiga-works (accessed 7/23/2015).
AMG 1067	IMS Health Data 2012-2015 for Zytiga®, Xtandi® and Jevtana®

TABLE OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotrophic hormone
AR	Androgen receptor
CRPC	Castration-resistant prostate cancer
mCRPC	Metastatic Castration-resistant prostate cancer
CYP17	17 α -hydroxylase/C _{17,20} -lyase
DHT	Dihydrotestosterone
HWT mice	Human wild type mice
IDS	Information Disclosure Statement
LH	Luteinizing hormone
NDA	New Drug Application
POSA	Person of Ordinary Skill in the Art
PSA	Prostate-specific antigen
RCE	Request for Continued Examination

CHALLENGED CLAIMS OF U.S. PATENT NO. 8,822,438

1. A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

2. The method of claim 1, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.

3. The method of claim 2, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is from about 500 mg/day to about 1500 mg/day.

4. The method of claim 3, wherein the therapeutically effective amount of abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.

5. The method of claim 1, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is administered in at least one dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, wherein therapeutically effective amount of prednisone is from about 0.01 mg/day to about 500 mg/day.

7. The method of claim 6, wherein therapeutically effective amount of prednisone is from about 10 mg/day to about 250 mg/day.

8. The method of claim 7, wherein therapeutically effective amount of prednisone is about 10 mg/day.

9. The method of claim 1, wherein the therapeutically effective amount of prednisone is administered in at least one dosage form comprising about 5 mg of prednisone.

10. The method of claim 1, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

11. The method of claim 10, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

12. The method of claim 1, wherein said prostate cancer is refractory prostate cancer.

13. The method of claim 2, wherein refractory prostate cancer is not responding to at least one anti-cancer agent.

14. The method of claim 13, wherein at least one anti-cancer agent comprises a hormonal ablation agent, an anti-androgen agent, or anti-neoplastic agent.

15. The method of claim 14, wherein the hormonal ablation agent comprises deslorelin, leuprolide, goserelin, or triptorelin.

16. The method of claim 14, wherein the anti-androgen agent comprises bicalutamide, flutamide, or nilutamide.

17. The method of claim 14, wherein the antineoplastic agent comprises docetaxel.

18. The method of claim 12, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

19. The method of claim 18, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

20. The method of claim 17, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438

I. INTRODUCTION

Amerigen Pharmaceuticals, Ltd. ("Petitioner") petitions for *Inter Partes* Review of claims 1 - 20 of U.S. Patent No. 8,822,438 to Auerbach *et al.* ("the '438 patent") (AMG Ex. 1001), which is assigned to Janssen Oncology, Inc. ("Janssen"), under 35 U.S.C. §§ 311-319 and 37 C.F.R. Part 42 and a determination that all claims (1-20) of the '438 patent be canceled as unpatentable.

II. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

Petitioner provides the following mandatory notices under 37 C.F.R. §§ 42.8(a)(1) and 42.8(b).

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner Amerigen Pharmaceuticals, Ltd. is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

To the best of Petitioner's knowledge, the following litigations or other related matters related to the '438 patent that would affect, or be affected by, a decision in this proceeding are pending:

BTG International Limited et al. v. Actavis Laboratories FL, Inc. et al., 15 cv 81079-DMM (Southern District of Florida).

BTG INTERNATIONAL LIMITED et al. v. Actavis Laboratories FL, Inc., Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York, LLC.

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Apotex Corp., Apotex Inc., Citron Pharma LLC,, Dr. Reddy's Laboratories, Inc., Dr. Reddy's Laboratories, Ltd., Hikma Pharmaceuticals, LLC., Mylan Pharmaceuticals Inc., Mylan, Inc., Par Pharmaceuticals Companies, Inc., Par Pharmaceuticals, Inc., Sun Pharmaceuticals Industries, Inc., Sun Pharmaceuticals Industries, Ltd, Teva Pharmaceuticals USA, Inc., West-Ward Pharmaceuticals Corp., Wockhardt BIO AG, Wockhardt Ltd., Wockhardt USA LLC, 15 cv 5909-KM-JBC (District of New Jersey)

C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Lead Counsel	Back-Up Counsel
William Hare (Reg. No. 44,739) McNeely Hare & War LLP 12 Roszel Road, Suite C104, Princeton, NJ 08540 Telephone: (202) 640-1801 Fax: (202) 478-1813 bill@miplaw.com	Gabriela Materassi (Reg. No. 47,774) McNeely Hare & War LLP 12 Roszel Road, Suite C104, Princeton, NJ 08540 Telephone: (347) 684-4154 Fax: (202) 478-1813 materassi@miplaw.com

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Documents may be delivered by hand to the addresses of lead and back-up counsel above. Petitioner consents to electronic service by e-mail at the above listed email addresses of Lead and Back-Up Counsel (bill@miplaw.com and materassi@miplaw.com).

E. Service on Patent Owner Under 37 C.F.R. § 42.106(a) and 42.105(a)

Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438

This petition is being served by Express Mail on Janssen Oncology, Inc., owners of the ‘438 Patent, at their addresses of record according to the USPTO PAIR database: Janssen Oncology, Inc., 10990 Wilshire Blvd., Suite 1200, Los Angeles, CA 90024; and Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003.

III. GROUNDS FOR STANDING (37 C.F.R. §§ 42.101 and 42.104)

Petitioner is eligible under 37 C.F.R. § 42.101 to file a petition to initiate an *inter partes* review of the ‘438 patent because: (1) the Petitioner does not own the ‘438 patent; (2) prior to the date this Petition was filed, neither the Petitioner nor any real party-in-interest filed a civil action challenging the validity of a claim of the ‘438 patent; (3) this Petition has been filed less than one year after the date on which Petitioner, a real party-in-interest, or a privy of the Petitioner were served with a complaint alleging infringement of the ‘438 patent; and (4) neither Petitioner, any real party-in-interest, nor any privies of Petitioner, are estopped from challenging the claims on the grounds identified in this Petition.

Petitioner certifies under 37 C.F.R. § 42.104 that the ‘438 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in the petition.

This Petition is filed in accordance with 37 CFR § 42.106(a). Concurrently

Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438

filed herewith is a Power of Attorney and an Exhibit List per § 42.10(b) and § 42.63(e), respectively.

IV. PAYMENT OF FEES (37 C.F.R. § 42.103)

The required fee is paid via online credit card payment. The Office is authorized to charge any fee deficiencies and credit overpayments to Deposit Acct. No. 502923, Customer ID No. 32687.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(a))

Petitioner requests *inter partes* review and cancellation of claims 1-20. Petitioner's full statement of the reasons for the relief requested is set forth in detail in Section XI-XIII below.

VI. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner respectfully requests *inter partes* review and cancellation of claims 1-20 of the '438 Patent based on the grounds set forth in the table below:

Ground	Challenged Claims	Statutory Basis	References
1	1-20	§ 103	O'Donnell in view of Gerber
2	1-4 and 6-11	§ 103	'213 patent in view of Gerber

Sections XI-XIII below explain how the '438 patent claims are unpatentable on the grounds listed above. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18

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(1966) (obviousness analysis evaluates the level of ordinary skill in the art; the scope and content of the prior art; whether any differences between the prior art and the claims would have been obvious to the skilled artisan; and secondary considerations).

In support of these grounds for unpatentability, Petitioner submits the expert declaration of Dr. Scott Serels, M.D., (AMG Ex. 1002 (“Serels Declaration”)) to discuss the relevant field and art in general, and the factual and opinion bases underlying Petitioner’s Grounds 1 and 2 for the *Graham* factors other than commercial success. Petitioner also submits the expert declaration of economics expert Dr. DeForest McDuff, PhD (AMG Ex. 1017 (“McDuff Declaration”)) on the secondary considerations of the *Graham* factors.

Petitioner also relies on the other Exhibits set forth in the concurrently filed Listing of Exhibits.

VII. INTRODUCTION AND SUMMARY OF ARGUMENT

The claims of the ‘438 patent are directed to treating prostate cancer by administering therapeutically effective amounts of abiraterone acetate, a 17 α -hydroxylase/C_{17,20}-lyase inhibitor ("CYP17 inhibitor"), in combination with prednisone, a glucocorticoid. The prior art taught use of abiraterone acetate as an effective anti-cancer agent which suppresses testosterone synthesis in prostate cancer patients. AMG Ex. 1002, Serels Decl. ¶¶ 26, 45, 56, 58. It was known that

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testosterone promoted prostate cancer proliferation and progress so that to treat prostate cancer, testosterone synthesis must be suppressed.

However, it was known that in using a CYP17 inhibitor to reduce testosterone synthesis, the CYP17 inhibitor also undesirably suppressed the production of cortisol, a glucocorticoid, which is necessary for other biochemical cycles in the body and its reduced production caused adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. To address the suppressed synthesis of cortisol, the prior art also taught that concomitant glucocorticoid replacement therapy might be necessary when administering abiraterone to treat prostate cancer in a patient, and that this was common practice in the treatment of prostate cancer with ketoconazole, another CYP17 inhibitor. AMG Ex. 1002, Serels Decl. ¶¶ 32, 34, 48.

The prior art also taught that abiraterone was a more effective CYP17 inhibitor than ketoconazole. For example, the prior art taught that abiraterone acetate was more effective in decreasing testosterone levels in a mammal than ketoconazole. AMG Ex. 1002, Serels Decl. ¶¶ 36, 45. The prior art also taught that the combination of ketoconazole and prednisone was a safe and effective treatment for refractory metastatic prostate cancer. AMG Ex. 1002, Serels Decl. ¶48.

One of skill in the art would have combined abiraterone acetate and prednisone based on teachings of O'Donnell in view of Gerber and/or the '213

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patent in view of Gerber for a safe and effective treatment of prostate cancer with a reasonable expectation of success because the prior art taught abiraterone acetate as a more effective CYP17 inhibitor than ketoconazole and the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer. AMG Ex. 1002, Serels Decl. ¶¶45-49.

There are no secondary considerations of commercial success that overcome obviousness. The claims of the application resulting in the '438 patent were repeatedly rejected for obviousness until the Examiner allowed the claims based on the purported "unexpected commercial success" of Zytiga®, the brand name under which abiraterone acetate is marketed in the United States by the Assignee. In particular, the Examiner's allowance of the claims based on secondary considerations of commercial success of Zytiga® was in error because Applicants failed to show the necessary nexus between the claimed invention (which is directed to method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga®.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '438 patent, the scientific field relevant is oncology or urology. AMG Ex. 1002, Serels Decl. ¶8. A person of ordinary skill in the art

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would be a physician specializing in urology or oncology, or holding a Ph.D. in pharmacology, biochemistry or a related discipline. AMG Ex. 1002, Serels Decl. ¶8. Additional experience could substitute for the advanced degree. AMG Ex. 1002, Serels Decl. ¶8. To the extent necessary, one of skill in the art may collaborate with one or more other persons of skill in the art for one or more aspects with which the other person may have expertise, experience and/or knowledge that was obtained through his or her education, industrial or academic experiences. AMG Ex. 1002, Serels Decl. ¶9. For example, one of skill may consult with an enzymologist and/or molecular biologist and thus may rely on the opinions of such specialists in evaluating the claims. AMG Ex. 1002, Serels Decl. ¶10.

IX. U.S. PATENT NO. 8,822,438 AND ITS FILE HISTORY**A. Specification of the ‘438 Patent**

The “Background” section describes prostatectomy and radiotherapy, a primary course of treatment for patients diagnosed with organ-confined prostate cancer, as being highly invasive and ineffective on metastasized prostate cancer. In addition, the specification states that these localized treatments are not effective on prostate cancer after it has metastasized; and that, moreover, a large percent of individuals who receive such localized treatments will suffer from “recurring cancer.” The specification states that another treatment option for prostate cancer,

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hormone therapy, is less invasive than surgery and has fewer side effects.

However, the specification notes that hormone therapy is not equally effective in all patients thus treated; and some patients suffer from relapsing or recurring cancer after hormone therapy. AMG Ex. 1001, Col. 1, ll. 25-64.

The “Summary of the Invention” section describes various embodiments of the invention being directed to methods and compositions of treating a refractory cancer in a patient, involving administration of an effective amount of a CYP17 inhibitor and an effective amount of another anticancer agent such as mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including prednisone or dexamethasone. AMG Ex. 1001, Col. 2, l. 9 – col. 3, l. 20.

The “Definitions” section defines “17 α -hydroxylase/C_{17,20}-lyase inhibitor” as an inhibitor of the enzyme “17 α -hydroxylase/C_{17,20}-lyase” (an enzyme involved in testosterone synthesis). AMG Ex. 1001, Col. 3, l. 66 – col. 4, l. 7. The terms “treat,” “treating” and “treatment” are defined as including the “eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.” AMG Ex. 1001, Col. 3, ll. 46-50. The term “anti-cancer agent” is defined as referring to “any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells.”

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AMG Ex. 1001, Col. 4, ll. 8-16. The term “refractory cancer” is defined as “cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment.” AMG Ex. 1001, Col. 4, ll. 23-27.

The “Detailed Description of the Invention” section refers to U.S. Patent No. 5,604,213 (“Barrie *et al.*”, AMG Ex. 1005) for its disclosure of CYP17 inhibitors being “shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer.” AMG Ex. 1001, Col. 5, ll. 23-29. The specification provides a list of various CYP17 inhibitors including abiraterone (3 β -ol-17-(3-pyridyl) androsta-5,16-diene). AMG Ex. 1001, Col. 5, ll. 30-40.

According to the specification, the CYP17 inhibitors may also be administered or combined with steroids, such as corticosteroids or glucocorticoids including hydrocortisone, prednisone, or dexamethasone, in the same or different compositions. AMG Ex. 1001, Col. 10, ll. 15-19. A single unit solid oral dosage forms may contain about 50 mg to about 300 mg of abiraterone acetate and about 0.5 to 3 mg of a steroid, e.g., glucocorticoid, optionally with additional excipients. AMG Ex. 1001, Col. 10, ll. 42-50. Suitable daily dosages of CYP17 inhibitors according to the ‘438 patent can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day. AMG Ex. 1001, Col. 11, ll. 33-43.

According to the specification, the method for the treatment of cancer can

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comprise administering an amount of about 50 mg/day to about 2000 mg/day or about 500 mg/day to about 1500 mg/day of abiraterone acetate, and an amount of about 0.01 mg/day to about 500 mg/day or about 0.5 mg/day to about 25 mg/day of glucocorticoid, such as hydrocortisone, dexamethasone or prednisone. AMG Ex. 1001, Col. 13, ll. 6-39.

One example of a composition according to the invention comprises a CYP17 inhibitor such as abiraterone acetate in combination with a steroid, such as hydrocortisone, prednisone or dexamethasone. The composition can comprise about 50-500 mg of abiraterone acetate, and about 0.25-3.5 mg of steroid. AMG Ex. 1001, Col. 15, ll. 52-66.

B. File History of the '438 Patent

The '438 patent has a lengthy and involved prosecution. The application resulting in the '438 Patent was filed on February 24, 2011 and assigned Application No. 13/034,340. The application was filed as a continuation of Application No. 11/844,440, filed on August 24, 2011, which claims priority to Provisional Application No. 60/921,506, filed on August 25, 2006.

In an Office Action dated November 25, 2011, the Examiner imposed restriction between the claims of Group I (claims 1-26, drawn to a method for treating cancer); and the claims of Group II (claims 27-36, drawn to a composition). In a Response dated December 21, 2011, Applicants cancelled the

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pending claims, and elected the invention of Group I, represented by newly presented claims 37-56. Newly presented claims 37-56 are substantively similar to claims 1-20 of the '438 patent as issued.

In an Office Action dated February 3, 2012, all pending claims 37-56 were rejected for obviousness over O'Donnell (AMG Ex. 1003) in view of Tannock (AMG Ex. 1006). The Examiner characterized O'Donnell as disclosing the CYP17 inhibitor abiraterone acetate being used to suppress testosterone levels in prostate cancer patients. February 3, 2012 Office Action (AMG Ex. 1007) at p. 2. Tannock was cited for teaching 10 mg prednisone "in combination with another anti-cancer drug [i.e., mitoxantrone] as effective in treating refractory hormonal-resistant prostate cancer." AMG Ex. 1007 at p. 3.

In a Response dated July 3, 2012, Applicants argued that "nothing in the art teaches or suggests that abiraterone acetate in combination with prednisone would be a particularly useful combination for cancer treatment." July 3, 2012 Response (AMG Ex. 1008) at p. 2. Applicants further argued that "even if one of ordinary skill would have been motivated to combine both modes of treatment, the claimed invention produces unexpected results." AMG Ex. 1008 at p. 2.

Applicants provided as evidence to support unexpected results the disclosure of Sartor, *Nature Reviews Clinical Oncology*, 8:515-516 (2011), reporting data from a clinical study of patients with metastatic castration-resistant prostate cancer

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("mCRPC") previously treated with chemotherapy who were treated with the combination of abiraterone and prednisone or prednisone alone. Applicants described Sartor as teaching that "abiraterone plus prednisone prolongs overall survival relative to prednisone alone." AMG Ex. 1008 at p. 2.

Applicants also argued that worldwide sales data for Zytiga® (the trade name under which abiraterone acetate is marketed) were evidence of purported commercial success of the claimed invention. According to the Applicants, sales of Zytiga® were evidence of the commercial success of the claimed combination because the approved label for Zytiga® directs patients to use Zytiga® in combination with prednisone. AMG Ex. 1008 at p. 3.

In a Final Office Action dated September 11, 2012, the Examiner maintained the rejection of the claims over O'Donnell and Tannock. In a Request for Continued Examination ("RCE") and Response dated January 11, 2013, Applicants once again argued unexpected results and provided another reference, Ryan *et al.*, *New Eng. J. of Med.*, 368:138-148 (2012) (AMG Ex. 1009), purporting to show unexpected results of the claimed invention over prednisone. For example, Applicants argued an "unexpected survival benefit of abiraterone with prednisone" over "prednisone alone." January 11, 2013 Response (AMG Ex. 1010) at 7.

In a Final Office Action dated March 4, 2013, the Examiner continued to maintain the obviousness rejection of claims 37-56 over O'Donnell and Tannock.

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The Examiner explained that "since abiraterone acetate provide a new mechanism of action in treating prostate cancer and prednisone is known to be useful for treating cancer, concomitant employment of both compounds into a single method useful for the same purpose, treating prostate cancer, would be considered *prima facie* obvious." Office Action dated March 4, 2013 (AMG Ex. 1011) at p. 3.

However, as explained in the Serels Declaration, the Examiner's stated reasons for combining both compounds into a single method included incorrect facts. First, abiraterone acetate did not provide a new mechanism of action. As explained above and set out in O'Donnell, both ketoconazole and abiraterone were known CYP17 inhibitors acting by the same mechanism. Second, prednisone was not accepted as being useful for treating cancer. As explained in the Serels Declaration (AMG Ex. 1002, ¶¶74, 79, 80), in the 1980s there was a belief that prednisone might be useful for treating prostate cancer. However, at the time of filing of the '438 patent, it was known that prednisone was not effective as an anti-cancer agent for prostate cancer but it was common practice to co-administer a glucocorticoid such as prednisone with a CYP17 inhibitor *for glucocorticoid replacement*. AMG Ex. 1002, Serels at ¶¶34, 48, 68.

In a Notice of Appeal and Response dated June 4, 2013, Applicants reiterated their argument of Tannock purportedly teaching away from the use of prednisone with abiraterone acetate because Tannock teaches that "there was no

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significant difference in overall survival between prednisone alone and prednisone plus the cancer agent mitoxantrone.” Response dated June 4, 2013 (AMG Ex. 1012) at p. 6. Applicants argued that one of skill in the art, reading Tannock, would have expected “there to be no difference in survival between one cancer agent alone, and the same cancer agent in combination with prednisone.” AMG Ex. 1012 at p. 6.

Applicants also provided the FDA approval label for Zytiga™ and argued that "taking Zytiga in accordance with the approved label [*i.e.*, in combination with prednisone] represents a commercial embodiment of the presently claimed invention." AMG Ex. 1012 at p. 7. Applicants also submitted a news release from FDA announcing that Zytiga was approved for the additional indication for use in prostate cancer patients prior to receiving chemotherapy as purporting to provide additional evidence of commercial success of the claimed combination. AMG Ex. 1012 at p. 7.

Applicants once again argued commercial success, this time based on market share data for Zytiga®, and a presentation entitled “Pharmaceuticals Commercial Overview” by Joaquin Duato, Worldwide Chairman, Pharmaceuticals, Janssen, dated May 2013 ("Duato presentation"), which characterized Zytiga as having the most successful launch of an oral oncology product ever “Zytiga®: Most Successful Oral Oncology Launch in History.” AMG Ex. 1012 at p. 7, slide 11.

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Applicants specifically pointed to a slide showing a 70% market share for Zytiga in July 2012 for “chemo refractory prostate cancer patients.” Applicants argued that the Duato presentation showed that despite another product, Xtandi®, being introduced in August 2012, as of April 2013, Zytiga was still the market leader with 57% market share in “chemo-refractory prostate cancer patients.” AMG Ex. 1012 at p. 7, slide 12. Applicants concluded that “not only is ZYTIGA the most successful oral oncology launch in history, two years after its initial approval it is still the market leader for chemo refractory prostate cancer despite an earlier introduced therapy [*i.e.*, Jevtana®] and a later introduced therapy [*i.e.*, Xtandi®].” AMG Ex. 1012 at p. 8. Applicants argued that “this commercial success [of Zytiga] demonstrates the non-obviousness of the presently claimed invention.” AMG Ex. 1012 at p. 8.

In a Notice of Allowance dated July 3, 2013, all pending claims were allowed with the Examiner providing the following reason for allowance: “The *unexpected commercial success* of the launch of the drug obviates the rejection under 35 USC 103(a).” Notice of Allowance dated July 3, 2013 at 2 (emphasis added) (AMG Ex. 1013).

In an Information Disclosure Statement (“IDS”) dated October 3, 2013 submitted with an RCE, Applicants provided a number of non-patent literature documents, following which a second Notice of Allowance was issued on October

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25, 2013. Among the references listed in the October 3, 2013 IDS was Gerber (AMG Ex. 1004). A second Notice of Allowance issued dated October 25, 2013 wherein the Examiner stated in the Notice of Allowability that the reasons for allowance were "essentially the same" as in the previous notice. AMG Ex. 1013, at p. 2.

A second IDS submitted with a second RCE and listing additional non-patent documents was filed by Applicants on January 10, 2013, following which a third Notice of Allowance was issued on February 11, 2014. The Examiner again stated in the Notice of Allowability that the reasons for allowance were "essentially the same as in the initial notice" and further stated that "the commercial success of the combination of prednisone and abiraterone to treat prostate cancer obviate the rejection under 35 U.S.C. 103(a)." AMG Ex. 1015 at p. 2.

A third IDS, dated May 9, 2014, listed a number of additional references. A fourth IDS, dated May 30, 2014, provided statements of opposition filed in the European Patent Office for a counterpart foreign application of the '438 patent; Applicants' response to the opposition; and a number of additional references. A fourth Notice of Allowance was issued on June 2, 2014, reiterating the same grounds for allowance as the previous notice. AMG Ex. 1016.

X. CLAIM CONSTRUCTION (37 C.F.R. §§ 42.100(b), 42.104(b)(3))

Pursuant to 37 C.F.R. § 42.100(b), a claim in an unexpired patent is given its

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broadest reasonable interpretation in light of the specification. Petitioners submit for purposes of this petition only that the terms in the claims of the '438 patent do not have any special meanings and are presumed to take on their broadest reasonable meaning consistent with the understanding of a person of ordinary skill in the art ("POSA") when read in light of the '438 patent's specification. Because the claim construction standard in an *inter partes* review is different than that used in litigation, Petitioners reserve the right to present different constructions of terms in litigation under claim construction standards appropriate for those cases. *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

The following terms in the claims are defined for purposes of this petition as they are defined in the specification of the '438 patent:

1. The claim terms "treat," "treating" and "treatment" should be construed as those terms are defined in the specification of the '438 Patent to mean the "eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer." AMG Ex. 1001, col. 3, ll. 46-50.

2. The claim term "anti-cancer agent" should be construed as defined in the specification of the '438 patent as referring to "any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells." AMG Ex. 1001, col. 4, ll. 8-16.

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3. The claim term “refractory cancer” should be construed as defined in the specification of the '438 patent to mean “cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment.” AMG Ex. 1001, col. 4, ll. 23-27.

XI. SCOPE AND CONTENT OF THE PRIOR ART

A. Overview

The '438 patent has a single independent claim that is directed to a method for treating prostate cancer comprising administering therapeutically effective amounts of abiraterone acetate, a CYP17 inhibitor, in combination with prednisone, a glucocorticoid. However, the prior art taught use of abiraterone acetate as an effective anti-cancer agent which suppresses testosterone synthesis in prostate cancer patients. AMG Ex. 1002, Serels Decl. at ¶¶26, 27, 36, 45. The prior art also taught that concomitant glucocorticoid replacement therapy might be necessary when administering abiraterone to treat prostate cancer in a patient, and that this was common practice in the treatment of prostate cancer with ketoconazole, another CYP17 inhibitor. AMG Ex. 1002, Serels Decl. at ¶ 48, 56, 68.

The prior art also taught that abiraterone was a more effective CYP17 inhibitor than ketoconazole. For example, the prior art taught that abiraterone acetate was more effective in decreasing testosterone levels in a mammal than

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ketoconazole. AMG Ex. 1002, Serels Decl. at ¶¶36, 45, 49. The prior art also taught that the combination of ketoconazole and prednisone was a safe and effective treatment for refractory metastatic prostate cancer. AMG Ex. 1002, Serels Decl. at ¶¶35, 48.

One of skill in the art would have combined abiraterone acetate and prednisone based on teachings of O'Donnell and Gerber and/or the '213 patent and Gerber for a safe and effective treatment of prostate cancer with a reasonable expectation of success because the prior art taught the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer. AMG Ex. 1002, Serels Decl. at ¶¶48, 49.

During prosecution, after numerous rejections for obviousness, the Applicants argued that unexpected results rebutted the *prima facie* case of obviousness made by the Examiner. The Applicants argued that the cited prior art did not teach or suggest that abiraterone acetate in combination with prednisone would be “a particularly useful combination for cancer treatment.” AMG Ex. 1008 at p. 2. They further argued that commercial success of Zytiga® (the trade name under which abiraterone acetate is marketed) was evidence of non-obviousness of the claimed combination. AMG Ex. 1008 at pp. 2-3.

However, Gerber taught that some patients with hormone refractory metastatic prostate cancer could derive significant benefit from treatment with

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ketoconazole and prednisone. AMG Ex. 1002, Serels Decl. ¶35. Indeed, the administration of ketoconazole in combination with a glucocorticoid such as prednisone or hydrocortisone was a common practice at the time of the invention. AMG Ex. 1002, Serels Decl. ¶¶31-32, 34, 68. The Examiner did not consider Gerber during prosecution. Quite possibly, this is because Gerber was submitted *after* the initial notice of allowance, along with dozens of other references. Because the Examiner did not consider Gerber, the Examiner did not fully appreciate the obviousness of combining a CYP17 inhibitor (such as abiraterone) with a glucocorticoid (such as prednisone).

Applicants also argued that abiraterone and prednisone unexpectedly prolonged overall survival relative to prednisone alone, and that the prior art taught away from combining abiraterone with prednisone. AMG Ex. 1012 at p. 6. For example, in traversing repeated obviousness rejections over Tannock (AMG Ex. 1006), the Applicants argued that Tannock taught away from use of abiraterone with prednisone because it showed that there “was no significant difference in overall survival [between prednisone alone and prednisone plus the cancer agent mitoxantrone].” which would have led one of skill in the art to expect “no difference in survival between one cancer agent alone, and the same cancer agent in combination with prednisone.” AMG Ex. 1012 at p. 6.

This was an erroneous and misleading inference to make for at least two

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reasons: (i) the co-administration of prednisone with abiraterone was not intended to enhance the *anti-cancer* properties of abiraterone, already known in the art to be a very selective CYP17 inhibitor (and consequently a potent inhibitor of peripheral testosterone production), but rather *to reduce side effects* associated with administering abiraterone; and (ii) the proper comparison for overcoming obviousness over the prior art should have been whether there was any unexpected synergistic anti-cancer benefit of using *abiraterone in combination with prednisone* beyond the anti-cancer effect of administering *abiraterone alone*.

While the Examiner did not find Applicants' arguments regarding unexpected results persuasive, the Examiner also did not fully appreciate the obviousness of the claimed invention or the reason that the claimed invention does not produce unexpected results. For example, in a Final Rejection dated March 4, 2013 maintaining an obviousness rejection of the pending claims, the Examiner explained that "[s]ince abiraterone acetate provide a new mechanism of action in treating prostate cancer and prednisone is known to be useful in treating refractory prostate cancer, concomitant employment of both compounds into a single method useful for the same purpose, treating prostate cancer, would be considered *prima facie* obvious." AMG Ex. 1011 at p. 3. However, as explained below, CYP17 inhibitors were known in the art for treating prostate cancer, so that the mechanism of action of abiraterone acetate was not new. Additionally, it was known that co-

administering a glucocorticoid such as prednisone with a CYP17 inhibitor was necessary as hormone replacement therapy in order to reduce potential side effects of administering a CYP17 inhibitor, *not* to enhance an anti-cancer benefit.

Moreover, the Examiner committed error in allowing the claims based on the purported "unexpected commercial success" of Zytiga®, the brand name under which abiraterone acetate is marketed in the United States by the Assignee. In particular, the Examiner's allowance of the claims based on secondary considerations of commercial success of Zytiga® was in error because Applicants failed to show the necessary nexus between the claimed invention (which is directed to method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga®, which consists of abiraterone acetate.

B. Background of Prostate Cancer and Its Treatment

Prostate cancer is an androgen-dependent disease. AMG Ex. 1002, Serels Decl. at ¶13. The activation of androgen receptors ("AR") on prostate cells regulates the transcriptional activation of a wide variety of genes involved in promoting the progression and proliferation of prostate cancer. AMG Ex. 1002, Serels Decl. at ¶14. The two most important androgens responsible for activating the AR are testosterone and its derivative dihydrotestosterone ("DHT"). Testosterone is synthesized primarily in the testes and the adrenals.

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The treatment options for treating prostate cancer depend to a great extent on whether the prostate cancer is confined or localized to the prostate or whether it has spread to other organs (*i.e.*, metastasized) from the prostate. The goal of treating primary prostate cancer (*i.e.*, prostate cancer localized to the prostate) is to interfere with the proliferation of prostate cancer cells by interrupting production of testosterone and DHT in the testes, or interfering with their function of binding with receptors on prostate cancer cells. However, a significant number of patients do not respond to localized therapy to suppress testosterone, and consequently develop metastatic prostate cancer. AMG Ex. 1002, Serels Decl. at ¶16.

The treatment of metastatic prostate cancer requires systemic therapy. An important goal in treating metastatic prostate cancer patients who have undergone localized androgen ablation is to reduce baseline circulating testosterone levels. A substantial amount of extratesticular testosterone is produced in the adrenal glands. The first-line treatment for metastatic prostate cancer patients since at least the 1980's has involved systemic suppression of extratesticular testosterone production by the peripheral organs, including the adrenal glands, and is commonly referred to as hormone therapy. AMG Ex. 1002, Serels Decl. at ¶18.

In almost all cases, patients with metastatic prostate cancer develop what is referred to as refractory or castration-resistant prostate cancer ("CRPC"), *i.e.*, prostate cancer that does not respond to a reduction in testosterone levels by

surgical or chemical means and resumes growth. AMG Ex. 1002, Serels Decl. at ¶21.

The treatment of metastatic refractory prostate cancer typically also comprises the use of secondary hormone therapy to further reduce testosterone production, usually in combination with anti-androgen therapy. AMG Ex. 1002, Serels Decl. at ¶22.

CYP17 inhibitors were known in the art to be useful in the treatment of androgen-dependent cancers, including prostate cancer, by contributing to suppression of peripheral androgen production. Ketoconazole, a non-specific inhibitor of 17- α hydroxylase, an enzyme critical to steroid synthesis, was commonly used off-label in combination with prednisone as a second-line treatment for metastatic refractory prostate cancer at the time of the invention of the '438 patent. AMG Ex. 1002, Serels Decl. at ¶23.

Like ketoconazole, abiraterone is a CYP17 inhibitor. AMG Ex. 1003, (O'Donnell); AMG Ex. 1002, Serels Decl. at ¶¶36, 45. CYP17 inhibitors were known to inhibit CYP17, an enzyme that is critical to androgen synthesis in both the testes and the adrenal cortex. While the CYP17 enzyme is essential for androgen biosynthesis, it also plays an important role in the production of cortisol, a glucocorticoid that is critical to basic metabolic functions including the formation of glucose, cardiovascular function, and the activation of the anti-stress

and inflammatory pathways. AMG Ex. 1002, Serels Decl. at ¶28.

When a CYP17 inhibitor is administered to suppress androgen synthesis, as an undesired side effect cortisol production is compromised (*e.g.*, reduced), which interferes with the negative feedback mechanism that usually maintains cortisol levels within the normal physiological range. This results in the pituitary gland producing more adrenocorticotrophic hormone (“ACTH”) to stimulate greater production of glucocorticoids, which are formed from ACTH, in part, by a reaction involving CYP17. However, in the presence of a CYP17 inhibitor, the conversion in the CYP17 pathway from ACTH to cortisol cannot occur. AMG Ex. 1002, Serels Decl. at ¶30.

It was known that CYP17 inhibition of cortisol increased ACTH drive (*i.e.*, increased ACTH production), which resulted in a corresponding increase in mineralocorticoids. An increase in mineralocorticoids beyond normal levels, known as “mineralocorticoid excess,” was known to have adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. AMG Ex. 1002, Serels Decl. at ¶31. It was general knowledge in the art to administer a glucocorticoid, such as prednisone or hydrocortisone, to a patient with ACTH drive, such as a patient administered a CYP17 inhibitor, to reduce ACTH drive, and consequently, reduce mineralocorticoid excess. AMG Ex. 1002, Serels Decl. at ¶32. Therefore, in a patient being treated for prostate

cancer with a CYP17 inhibitor such as ketoconazole, a patient would have been concomitantly administered a glucocorticoid such as prednisone for the purpose of reducing the side effects associated with increased ACTH drive that result from the CYP17 inhibitor, rather than treating prostate cancer itself. AMG Ex. 1002, Serels Decl. at ¶34.

It was known that administration of ketoconazole resulted in adverse side effects including high blood pressure, hypokalemia and swelling associated with ACTH drive and mineralocorticoid excess. AMG Ex. 1002, Serels Decl. at ¶34. Therefore, it was standard practice in the art to co-administer a glucocorticoid when using ketoconazole to treat patients with refractory metastatic prostate cancer. AMG Ex. 1002, Serels Decl. at ¶34.

One of skill in the art would have expected that administering abiraterone, an even more potent inhibitor of CYP17 than ketoconazole, to treat prostate cancer in a patient might also require co-administration of a glucocorticoid, such as prednisone. One of skill in the art would therefore have appreciated that the co-administration of prednisone with abiraterone was not intended to enhance the anti-cancer effect of abiraterone. Instead, one of skill in the art would have expected that the co-administration of prednisone with abiraterone would improve the safety and tolerability of administering abiraterone by reducing the potential for side effects associated with the administration of a CYP17 inhibitor. AMG Ex. 1002,

Serels Decl. at ¶34.

C. Prior Art References

1. In 2004, O'Donnell Described the Administration of Abiraterone Acetate as More Effective for Treating Metastatic Refractory Prostate Cancer than Ketoconazole, and Possibly Requiring Concomitant Glucocorticoid Replacement Therapy

O'Donnell, A. *et al.*, "Hormonal impact of the 17 α -hydroxylase/C17-20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer," *British J. of Cancer*, 90:2317-2325 (2004), ("O'Donnell," "AMG Ex. 1003"), published on May 18, 2004. O'Donnell is prior art to the '438 patent under at least 35 U.S.C. §102(b) (pre-AIA) because it was published on May 18, 2004, more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the '438 patent.

O'Donnell teach that abiraterone acetate is a CYP17 inhibitor that suppresses testosterone synthesis in patients with prostate cancer. *Abstract*. O'Donnell report that repeated treatment of male patients with prostate cancer with intact gonadal function (testicular function) with abiraterone acetate at a dose of 500-800 mg can successfully suppress testosterone levels to the castrate range. *Id.* O'Donnell also teach that the dose of abiraterone acetate administered to a particular patient may need to be adjusted in order to attain suppression of

testosterone levels at target levels. *See, e.g.*, AMG Ex. 1003, O'Donnell, *Abstract*; p. 2324. O'Donnell also report that adrenocortical suppression (*i.e.*, suppression of cortisol) may necessitate concomitant administration of replacement glucocorticoid with abiraterone acetate. *Id.*

O'Donnell report that as much as 10% of baseline circulating testosterone remains in castrated men due to peripheral conversion of adrenal steroids (DHEA and androstenedione) to testosterone. AMG Ex. 1003 at p. 2317. O'Donnell explain that this baseline circulating testosterone can activate overexpressed androgen receptors in hormone refractory tumors. AMG Ex. 1003 at p. 2317. O'Donnell also describe ketoconazole as an inhibitor of CYP17 that has shown anti-cancer activity for prostate cancer by decreasing the production of adrenal steroids. O'Donnell also describe abiraterone acetate as a more selective CYP17 inhibitor than ketoconazole of the CYP17 enzyme, which will more effectively decrease the production of adrenal steroids. AMG Ex. 1003 at p. 2318. They further report that the activity of ketoconazole as a second line agent in clinical trials among patients with prostate cancer supports the concept of a more selective inhibitor of the CYP17 enzyme. AMG Ex. 1003 at p. 2318.

O'Donnell describe the potential utility of abiraterone acetate as an effective anti-cancer agent for treating both castrate and noncastrate patients with advanced prostate cancer. O'Donnell report the results of three separate phase I studies

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wherein human patients with advanced prostate cancer, including patients who had progressed despite prior hormone and antiandrogen therapy, were treated with 500-800 mg abiraterone acetate and maintained testosterone suppression at target levels. AMG Ex. 1003 at pp. 2322-2323.

In one study, a single dose study in surgically or medically castrate male patients with advanced prostate cancer, a dose of 500 mg of abiraterone acetate was considered necessary to suppress testosterone to target levels. AMG Ex. 1003 at p. 2320.

In a second study, a single dose study involving non-castrate male patients with advanced prostate cancer, there appeared to be a steep dose-response relationship. They further report that at 500 mg of abiraterone acetate, treated patients showed persistent reductions in testosterone levels. AMG Ex. 1003 at p. 2323.

In a third study, a multidose study involving non-castrate male patients with advanced prostate cancer, O'Donnell report that a dose of at least 800 mg was required to maintain testosterone suppression at target levels. AMG Ex. 1003 at p. 2323.

In addition, O'Donnell report that repeated treatment of noncastrate patients with advanced metastatic prostate cancer with abiraterone acetate at a dose of 800 mg/day can successfully suppress testosterone levels to the castrate range. AMG

Ex. 1003 at pp. 2320-2322.

O'Donnell further report that from the repeat dose studies, it can be seen that a dose of at least 800 mg is required to maintain testosterone suppression at target levels in these patients. AMG Ex. 1003 at p. 2323.

O'Donnell also report that adrenocortical suppression (*i.e.*, the suppression of androgens secreted in the adrenal cortex) may necessitate concomitant administration of replacement glucocorticoid. AMG Ex. 1003 at p. 2323. In particular, they report that although baseline cortisol levels remained normal, “all patients treated at 500 mg and 800 mg in the multidose study developed an abnormal response to a short Synacthen test by Day 11, indicating a decrease in cortisol level.” O'Donnell further note that “some impact on cortisol levels was expected from the effect of abiraterone acetate on the steroid synthesis pathway.” AMG Ex. 1003 at p. 2323. O'Donnell further disclose that in the clinical use of ketoconazole, “it is common practice to administer supplementary hydrocortisone” and that this may prove necessary with abiraterone acetate. AMG Ex. 1003 at p. 2323. On the basis of the clinical evidence, O'Donnell report that the need for concomitant therapy of abiraterone acetate with a glucocorticoid needs to be further investigated. AMG Ex. 1003 at p. 2323.

2. In 1990, Gerber Disclosed the Use of Ketoconazole with Prednisone, a glucocorticoid, in Patients with Hormone

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Refractory Metastatic Prostate Cancer

Gerber G.S *et al.*, “Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic cancer,” *J. Urol.*, 144(5):1177-9 (November 1990), ("Gerber," "AMG Ex. 1004"), published November 1990. Gerber is prior art to the '438 patent under at least 35 U.S.C. §102(b) (pre-AIA) because it was published November 1990, more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the '438 patent. Gerber was submitted in a post-allowance IDS dated October 3, 2013. Therefore Gerber was of record, but not asserted by the Examiner nor argued by the Applicants, during prosecution of the '438 patent.

Gerber describe ketoconazole as a potent inhibitor of gonadal and adrenocortical steroid synthesis. Geber also describe that cytotoxic effects of ketoconazole on prostate cancer cells are known in the art and suggests its potential role in the treatment of prostate cancer. AMG Ex. 1004 at p. 1177.

Gerber teach the use of ketoconazole, a known CYP17 enzyme inhibitor and a potent inhibitor of gonadal and adrenocortical steroid synthesis, with prednisone in patients with hormone refractory metastatic prostate cancer. In particular, Gerber teach that patients with progressive prostate cancer despite androgen ablation, and therefore unresponsive to initial hormonal therapy, may benefit from the combination of ketoconazole and prednisone. AMG Ex. 1004 at p. 1179.

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Gerber note that the results of their study (which combined daily administration of 600-900 mg ketoconazole with the administration of 5 mg prednisone twice daily) show that 80% (12 out of 15) of patients with prostate cancer characterized by progressively increasing prostate specific antigen (“PSA”) levels experienced a decrease in PSA levels in response to treatment with ketoconazole and prednisone. AMG Ex. 1004 at pp. 1178-79. In addition, they report that 75% of the patients who had bone pain and/or other symptoms of advancing malignancy at the outset of the study had subjective improvement. AMG Ex. 1004 at p. 1178-79. They further report that 20% (3 out of 15) patients experienced a prolonged (8 to 10 months) favorable response to ketoconazole and prednisone based on persistently decreasing PSA levels and symptomatic improvement, including improvement in bone pain. AMG Ex. 1004 at pp. 1178-79. Gerber further report that this rate of response is similar to that found in studies that have used changes in measurable tumor size, bone scan abnormalities and acid phosphatase to assess response. Gerber thus conclude that their results show that some patients with progressive prostate cancer despite previous hormone therapy will derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy. AMG Ex. 1004 at p. 1179.

3. In 1997, the ‘213 Patent Disclosed Abiraterone Acetate, and Its Superiority over Ketoconazole in the Treatment of Prostate

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Cancer

U.S. Patent 5,604,213, issued to Barrie S.E. *et al.*, “Steroid dependent cancers such as prostate and breast cancer,” (“the ‘213 patent,” AMG Ex. 1005), was published on February 18, 1997. The ‘213 patent is prior art to the ‘438 patent under at least 35 U.S.C. §102(b) (pre-AIA) because it issued on February 18, 1997, more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the ‘438 patent. The ‘213 patent is incorporated by reference in the ‘438 patent, but it was neither argued nor disclosed in an IDS as relevant prior art during prosecution.

The ‘213 patent is one of the patents listed in the FDA Orange Book for Zytiga®. The ‘213 patent is not related to the ‘438 Patent and there is no overlap in inventorship between the ‘213 patent and the ‘438 Patent. The ‘213 patent is assigned on its face to British Technology Group, Ltd. Of note, the ‘213 patent was neither argued nor disclosed to the PTO in an IDS during prosecution.

The ‘213 patent relates to a novel class of 17-substituted steroids and their use in the treatment of androgen-dependent and estrogen-dependent disorders, especially prostatic cancer and breast cancer, respectively. AMG Ex. 1005 at Col. 1, ll. 11-14. The compounds of the ‘213 patent include abiraterone and acid addition salts and 3-esters of abiraterone (*see, e.g.*, AMG Ex. 1005 at Col. 5, ll. 21-26; Example 2 at col. 11, ll. 39-55), as well as abiraterone acetate in particular (*see,*

e.g., AMG Ex. 1005 at Example 1 at col. 10, ll. 62-11:35).

The '213 patent further disclose that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition comprising a therapeutically effective amount of the compound, which the '213 patent further discloses to be 20-800 mg/patient per day of abiraterone acetate. AMG Ex. 1005 at Col. 10, ll. 27-57.

The '213 patent discloses that the CYP17 enzyme complex is known to be essential for the biosynthesis of androgens and estrogens. The '213 patent further discloses that in the treatment of androgen-dependent disorders, especially prostatic cancer, there is a need for strong CYP17 inhibitors. AMG Ex. 1005 at Col. 1, ll. 19-22.

The '213 patent reports results from in vitro inhibition assays using tissue from the testes of previously untreated human patients undergoing orchidectomy for prostatic cancer. The assays compare the in vitro inhibition of 17α -hydroxyprogesterone androstenedione and testosterone production by some of the compounds of the invention, including abiraterone acetate (i.e., Example 1) with that of ketoconazole. The reported IC_{50} for abiraterone acetate is 0.0097 against lyase and 0.0130 against hydroxylase. By comparison, the reported IC_{50} for ketoconazole is 0.026 against lyase (or an order of magnitude higher than

abiraterone acetate) and 0.065 against hydroxylase. AMG Ex. 1005 at Col. 21, l. 25 - 25, l. 12.

The '213 patent further disclose the results of in vivo assays involving male human wild type ("HWT") mice that compare the effect on organ weight and production of testosterone and luteinizing hormone of administering abiraterone acetate and ketoconazole, respectively. The mice were tested for the presence of testosterone and luteinizing hormone. Post-mortem analyses of the adrenals, prostate, seminal vesicles, testes and kidneys were also conducted. The results show that the reductions in weight of all of the prostate, seminal vesicles, testes and kidneys were much greater for the test compounds of the invention than for ketoconazole. AMG Ex. 1005 at Col. 25, l. 41 - 26, l. 25; Table 3.

The '213 patent conclude that mammalian assays show that abiraterone acetate inhibits androgen, and particularly testosterone, synthesis. AMG Ex. 1005 at Col. 26, ll. 27-63; Table 4. The '213 patent further conclude that the decrease in testosterone levels resulting from the administration of abiraterone acetate was much more marked than for ketoconazole. AMG Ex. 1005 at Col. 26, ll. 32-38.

XII. EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claim 1

Claim 1 is obvious over O'Donnell in view of Gerber (Ground 1) or the '213 Patent in view of Gerber (Ground 2). Claim 1 is the only independent claim in the

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'438 patent. Claim 1 is directed to a method for treating prostate cancer in a human comprising administration of therapeutically effective amounts of abiraterone acetate, or a pharmaceutically acceptable salt thereof, and prednisone. Because both the use of abiraterone acetate to treat prostate cancer and the co-administration of prednisone in treatment of prostate cancer with a CYP17 inhibitor were present in the prior art with sufficient motivation to combine, claim 1 is obvious.

With respect to abiraterone acetate, both O'Donnell and the '213 patent teach that abiraterone acetate is a selective CYP17 inhibitor that is more effective in suppressing testosterone levels in a mammal in vivo than ketoconazole, a CYP17 inhibitor known in the art. AMG Ex. 1003, O'Donnell, at pp. 2318, 2322, 2323; 2325; Exhibit 1005, the '213 patent, col. 25, l. 13 - col. 26, l. 63. O'Donnell teaches that 500-800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including metastatic refractory prostate cancer. AMG Ex. 1003, O'Donnell, *Abstract*. The '213 patent discloses that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition. AMG Ex. 1005, the '213 patent, col. 10, ll. 47-56. The '213 patent further discloses that a therapeutically effective amount of abiraterone acetate comprises 20-800 mg/patient per day. AMG Ex. 1005, the '213 patent, col. 10, ll.

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55-56. The '213 patent also teaches that a salt of abiraterone acetate may be administered to a human patient with prostate cancer to treat prostate cancer in said human patient. AMG Ex. 1005, the '213 patent, col. 10, ll. 22-26.

It would have been obvious to administer abiraterone acetate to a human patient with a prostate cancer in light of the teachings of either O'Donnell or the '213 patent to administer a therapeutically effective amount of abiraterone acetate to treat a human patient with a prostate cancer.

Neither O'Donnell nor the '213 patent disclose co-administering prednisone with abiraterone acetate.

Although O'Donnell does not disclose administration of abiraterone acetate with prednisone, O'Donnell teaches that concomitant hormone replacement therapy with a glucocorticoid may be needed for continuous use of abiraterone acetate in treating a prostate cancer in a human patient. *See, e.g.*, AMG Ex. 1003, O'Donnell, *Abstract*, p. 2323. Gerber teaches that the combination of ketoconazole and prednisone is safe and effective in treating human patients with hormone-refractory advanced prostate cancer. Exhibit 1005, Gerber, *Abstract*, pp. 1177-1178, 1179. The motivation to add prednisone to a method of treating prostate cancer in a human patient that includes abiraterone acetate is clearly seen in Gerber who teaches that the administration of ketoconazole, a CYP17 inhibitor, in combination with 5 mg prednisone twice daily, is safe and effective in treating human patients with hormone-refractory prostate cancer. AMG Ex. 1004, Gerber, *Abstract* pp. 1177-

1178, 1179.

As such, the skilled artisan would expect that the addition of 10 mg of prednisone daily according to Gerber to the treatment regimen of O'Donnell also would be safe and effective in treating a prostate cancer, including prostate cancer refractory to anticancer therapy, including hormone and anti-androgen therapy.

Alternatively, the '213 patent teaches that abiraterone acetate is a CYP17 inhibitor that is more effective in suppressing testosterone levels in a mammal in vivo than ketoconazole, a CYP17 inhibitor known in the art. AMG Ex. 1005, the '213 patent, col. 25, l. 13 - col. 26, l. 63. Gerber teaches that the combination of ketoconazole and prednisone is safe and effective in treating human patients with hormone-refractory advanced prostate cancer. AMG Ex. 1004, Gerber, *Abstract*, pp. 1177-1178, 1179. The motivation to add prednisone to the method of treating prostate cancer of the '213 patent is clearly seen in Gerber who teaches that the administration of ketoconazole, a CYP17 inhibitor, in combination with 5 mg prednisone twice daily, is safe and effective in treating human patients with hormone-refractory prostate cancer. AMG Ex. 1004, Gerber, *Abstract* pp. 1177-1178, 1179. As such, the skilled artisan would expect that the addition of 5 mg twice daily prednisone to the treatment regimen of the '213 patent also would be safe and effective in treating a prostate cancer, including prostate cancer refractory to anti-cancer therapy, including hormone and anti-androgen therapy, in such patients.

Therefore, based on the teaching of either O'Donnell in view of Gerber or the

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‘213 patent in view of Gerber one of skill in the art would have been motivated to co-administer 10 mg/daily of prednisone with abiraterone acetate, a more selective CYP17 inhibitor than ketoconazole, in order to treat a human patient with prostate cancer, including prostate cancer refractory to previous anti-cancer therapy, including hormone and anti-androgen therapy, with a reasonable expectation that such treatment would be successful.

Claims 2-20 all depend directly or indirectly from claim 1, and include additional limitations of combinations of the following: i) the amount and/or dosage range of abiraterone acetate or a pharmaceutically acceptable salt thereof to be administered; ii) the amount and/or dosage range of prednisone to be administered; iii) the type of prostate cancer to be treated; or iv) whether the patient has been previously treated with another anti-cancer agent, where the additional anti-cancer agent may be a hormonal ablation agent, an anti-androgen agent, or an anti-neoplastic agent. For the reasons set forth above for claim 1 and additionally for the reasons set forth below, these additional categories of limitations also are obvious over O'Donnell in view of Gerber and/or the ‘213 patent in view of Gerber.

B. Claims 2 and 3

O'Donnell teaches that 500-800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including metastatic prostate cancer. *See, e.g.,* AMG Ex. 1003, O'Donnell, *Abstract*. The

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'213 patent teaches that a therapeutically effective amount of abiraterone acetate for treating prostate cancer in a human patient includes 20-800 mg/day. AMG Ex. 1005, the '213 patent, col. 10, ll. 47-56.

A therapeutically effective amount of 500-800 mg of abiraterone acetate as taught by O'Donnell or of 20-800 mg per day of abiraterone acetate as expressly taught in the '213 patent is within the range of "about 50 mg/day to about 2000 mg/day" (claim 2); and "about 500 mg/day to about 1500 mg/day" (claim 3). For the foregoing reasons, the daily dosage amounts and ranges of abiraterone acetate recited in these claims are disclosed both in O'Donnell and the '213 patent.

Therefore claims 2 and 3 are obvious over O'Donnell in view of Gerber (Ground 1) or the '213 patent in view of Gerber (Ground 2).

C. Claim 4

Although neither O'Donnell nor the '213 patent expressly teach an amount of abiraterone acetate of about 1000 mg/day as recited in claim 4, O'Donnell reports a dose of 500-800 mg/day of abiraterone acetate used in phase 1 human studies. AMG Ex. 1003, *Abstract*, p. 2318. The '213 patent discloses 20-800 mg/day of the drug. AMG Ex. 1005, the '213 patent, Col. 10, ll. 55-56. O'Donnell reports that a dose of 800 mg of abiraterone acetate can successfully suppress testosterone levels to the castrate range, but this level of suppression may not be sustained in all patients due to compensatory hypersecretion of luteinizing

hormone (“LH”). AMG Ex. 1003, O'Donnell, *Abstract*. O'Donnell concludes from the studies that in the face of increased LH, higher doses of abiraterone acetate may be required. *See, e.g.*, AMG Ex. 1003, O'Donnell, *Abstract*; p. 2324.

It would have been obvious to one of skill in the art to optimize the dosage range of abiraterone acetate to 1000 mg administered to treat prostate cancer in a human patient based on the teaching in O'Donnell that adjustments in the dosage amount of abiraterone acetate may be necessary to treat a patient. In addition, with respect to both O'Donnell and the '213 patent, optimizing the dosage range and dosage regimen of known active ingredients to be administered was considered well within the competence level of an ordinary skilled artisan in the pharmaceutical sciences as of at least 2006.

Based on the teachings of O'Donnell or the '213 patent, it would have been well within the skill of one in the art to optimize the amount of abiraterone acetate to be administered to treat prostate cancer in a human patient.

D. Claim 5

O'Donnell teaches that capsules containing 10, 50, 100 and 200 mg of abiraterone acetate were used in the three phase 1 clinical studies. It would have required only routine experimentation to increase the amount of abiraterone acetate in the capsules from 200 mg to 250 mg. Motivation for making this increase includes the starting dose of 500 mg in Study C and the use of 500 mg of

abiraterone in Studies A and B, which are a multiple of 250 mg. Therefore one of skill in the art would have made a 250 mg dosage form of abiraterone acetate for the convenience of dosing. For at least this reason claim 5 is obvious over O'Donnell in view of Gerber.

E. Claims 6-9

Claims 6-9 are directed to the amount or range of amount of prednisone administered: “about 0.01 mg/day to about 500 mg/day” (claim 6); “about 10 mg/day to about 250 mg/day” (claim 7); “about 10 mg/day” (claim 8); and “one dosage form comprising about 5 mg of prednisone” (claim 9). Each of these limitations is disclosed in Gerber, which teaches that the combination of ketoconazole, a CYP17 inhibitor, and 5 mg of prednisone twice daily is safe and effective in treating patients with hormone-refractory advanced prostate cancer. AMG Ex. 1004, Gerber, *Abstract*, pp. 1177-1178, 1179.

Claim 6 depends from claim 1 and is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of 10 mg/day of prednisone.

Claim 7 depends from claim 6 and narrows the range to about 10 mg/day to about 250 mg/day of prednisone. Because Gerber discloses 10 mg/day of prednisone, claim 7 is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of 10 mg/day of prednisone.

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Claim 8 depends from claim 7 and narrows the range to about 10 mg/day of prednisone. Because Gerber discloses 10 mg/day of prednisone, claim 8 is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of 10 mg/day of prednisone.

Claim 9 depends from claim 1 and requires the dosage form of prednisone to be about 5 mg. Gerber discloses administering 5 mg of prednisone twice daily, a dosage form of 5 mg of prednisone would have been obvious. As such, claim 9 is obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 is obvious and further for the disclosure in Gerber of administering 5 mg of prednisone.

F. Claim 10

Claim 10 depends from claim 1 and includes the limitation of about 500 mg/day to about 1500 mg/day of abiraterone acetate and about 0.01 mg/day to about 500 mg/day of prednisone. These limitations are recited in claims 3 and 6 respectively. Therefore claim 10 is invalid as being obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the reasons set out above for claims 1, 3 and 6.

G. Claim 11

Claim 11 depends from claim 10 and includes the limitations of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. These

limitations are recited in claims 4 and 8 respectively. Therefore claim 11 is invalid as being obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the reasons set out above for claims 1, 4, 8 and 10.

H. **Claims 12-16**

Claim 12 depends from claim 1 and includes the limitations of the prostate cancer being refractory prostate cancer. Claim 13 depends from claim 12 and requires the refractory prostate cancer to be not responding to at least one anti-cancer agent. Claim 14 depends from claim 13 and required the anti-cancer agent to be a hormonal ablation agent, an anti-androgen agent or an anti-neoplastic agent. Claim 15 depends from claim 14 and requires the hormonal ablation agent to be deslorelin, leuprolide, foserelin, or triptorelin. Claim 16 depends from claim 14 and requires the anti-androgen agent to be bicalutamide, flutamide, or nilutamide.

The patients in the phase I trial reported in O'Donnell were classified as having advanced or metastatic refractory prostate cancer. AMG Ex. 1001, O'Donnell, *Abstract*, pp. 2318-2319. In addition, one of the cohorts in O'Donnell had undergone hormone ablation surgery, *i.e.*, orchiectomy and all three cohorts of patients in O'Donnell had previously undergone hormone or anti-androgen therapy or both, and therefore had been previously treated with at least one anti-cancer agent, and in particular a hormone ablation agent or anti-androgen agent. AMG Ex. 1003, O'Donnell, *Abstract*; pp. 2318-2319, 2320. In Study A, all patients had received flutamide, an anti-androgen agent recited in

claim 16, and were receiving goserelin or leuporelin, hormone ablation agents.

Therefore claims 12 and 13 are obvious for the reasons set forth for claim 1 and additionally for the teaching in O'Donnell that abiraterone acetate may be administered to treat a human patient with metastatic prostate cancer that is refractory to at least one anti-cancer agent.

Claim 14 is obvious for the reasons set forth for claims 1, 12 and 13 and additionally for the teaching in O'Donnell that all three cohorts of patients in O'Donnell had previously undergone hormone or anti-androgen therapy or both.

Claim 15 is obvious for the reasons set forth for claims 1, 12, 13 and 14 and additionally for the teaching in O'Donnell that the patients in Study A had previous undergone hormone ablation therapy with goserelin or leuporelin.

Claim 16 is obvious for the reasons set forth for claims 1, 12, 13 and 14 and additionally for the teaching in O'Donnell that the patients in Study A had previous undergone anti-androgen therapy with flutamide.

I. Claim 17

Claim 17 depends from claim 14 and includes the limitations that the anti-neoplastic agent is docetaxel. O'Donnell does not expressly teach that abiraterone acetate may be administered to treat a human patient with metastatic prostate cancer that is refractory to an anti-neoplastic agent comprising docetaxel.

However, docetaxel was well known as an anti-cancer compound, and in particular, an anti-neoplastic agent at the priority date of the '438 Patent. For

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instance, U.S. Patent No. 5,688,977 (AMG Ex. 1029) which issued on November 18, 1997, states at col. 2, ll. 29-32, that docetaxel is an anti-cancer compound. And docetaxel in combination with prednisone was known to increase overall survival of patients with metastatic refractory prostate cancer, (AMG Ex. 1022, Tannock, Abstract), the first treatment known to do so, and was approved for the treatment of metastatic refractory prostate in 2004. *See*, AMG Ex. 1030, FDA News Release dated May 19, 2004. Therefore, claim 17 is obvious over O'Donnell in view of Gerber for the reasons set forth for claim 14 and additionally for the general knowledge in the art that docetaxel with prednisone was a first-line treatment for metastatic hormone refractory prostate cancer known to increase overall survival.

J. Claim 18

Claim 18 depends from claim 12 and includes the limitations from claim 10 of about 500 mg/day to about 1500 mg/day of abiraterone acetate and about 0.01 mg/day to about 500 mg/day of prednisone. Therefore claim 18 is invalid as being obvious over O'Donnell in view of Gerber for the reasons set out above for claims 10 and 12.

K. Claim 19

Claim 19 depends from claim 18 and includes the limitations from claim 11 of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. Therefore claim 19 is invalid as being obvious over O'Donnell in view of Gerber

for the reasons set out above for claims 11 and 18.

L. Claim 20

Claim 20 depends from claim 17 and includes the limitations from claim 11 of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. Therefore claim 20 is invalid as being obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 17.

XIII. SECONDARY CONSIDERATIONS DO NOT INDICATE THAT THE CLAIMS OF THE '438 PATENT ARE NON-OBVIOUS

To counter the *prima facie* evidence that all claims of the '438 patent are obvious, the patentee may try to rely on secondary considerations of non-obviousness. While any such evidence would be “insufficient” to “overcome the strong case of obviousness” here (*Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2008)), we nonetheless preliminarily address these alleged secondary considerations below, and reserve the right to respond to any arguments by the patentee asserted in this proceeding.

A. Applicants Did Not Offer Relevant Evidence of Commercial Success and the Examiner Issued the '438 Patent Based on the Erroneous Conclusion that the Asserted Commercial Success of Zytiga® Overcame the Obviousness of the Claimed Invention.

Applicants asserted during prosecution that commercial success of Zytiga®,

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the commercial product containing abiraterone acetate, was evidence of the non-obviousness of the claimed invention. AMG Ex. 1012 at p. 8. The Examiner erroneously concluded that the alleged “unexpected commercial success of the launch of the drug”, Zytiga®, obviated the obviousness rejection over O’Donnell and Tannock. AMG Ex. 1013, AMG Ex. 1014, AMG Ex. 1015. This was in error.

It is well settled that evidence of secondary considerations, such as commercial success, is only relevant to an obviousness analysis if the Patentees can show a direct link, or nexus, between the secondary consideration and the claims of the patent. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42, 227 USPQ 657, 673-674 n. 42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). In addition, that evidence must be commensurate in scope with the asserted claims. *Id.* Commercial success must be derived from the claimed invention. *Smith & Nephew, Inc. v. ConvaTec Technologies, Inc.*, Case Nos. IPR 13-00097 and IPR 13-00102 (PTAB, May 29, 2014); MPEP § 716.03(b). An applicant asserting commercial success to overcome an obviousness rejection bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success. MPEP § 716.03(I).

During prosecution, Applicants alleged that Zytiga's market shares of 70% in the "post-chemo" mCRPC market prior to the launch of Xtandi and 57% after the launch of Xtandi indicated that the claimed invention was a commercial

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success. AMG Ex. 1012 at p. 7, slide 12. Even assuming that the market definition Applicants used is accurate (and it is not), this information is insufficient as a matter of law because it fails to show any nexus between the claimed combination and the commercial performance of Zytiga®. In addition, as Dr. McDuff explains, evidence of Zytiga's® purported market share in a market Applicants define as the "post-chemo" mCRPC therapeutic market is deficient for a number of reasons. First, Applicants adduced no evidence that a market consisting only of "post chemo" mCRPC patients is the appropriate relevant market. As Dr. McDuff explains in his declaration, this market definition is much too narrow. AMG Ex. 1017, McDuff Decl. at ¶¶23-26. Using a market definition that includes all mCRPC patients immediately reduces Zytiga's market share substantially. AMG Ex. 1017, McDuff Decl. at ¶¶24-25.

Second, recent market data demonstrate a steep and continuous decline in Zytiga's market share post-Xtandi launch, and concurrent growth in Xtandi market share. AMG Ex. 1017, McDuff Decl. at ¶¶27-29. Dr. Serels explains that the perception among clinicians is that Xtandi has similar efficacy to, but a better safety profile than, Zytiga because Xtandi does not require co-administration of prednisone. AMG Ex. 1002, Serels Decl. at ¶¶85-87. The superior safety of Xtandi may account for Xtandi's growth in market share. In any event, this market shift is particularly notable in light of Applicants' argument during prosecution that

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Zytiga's continued commercial success after the introduction of Xtandi was further evidence of the commercial success of the invention. AMG Ex. 1017, McDuff Decl. at ¶¶23-30.

Lastly and most importantly, even assuming *arguendo*, that Zytiga's commercial performance, regardless of how broadly the relevant therapeutic market is defined, has been strong, any commercial success of Zytiga® is not shown to derive from the claimed invention, i.e., the combination of abiraterone acetate and prednisone. AMG Ex. 1017, McDuff Decl. at ¶¶31-35. Certainly, Applicants made no effort during prosecution to show any nexus between the claimed invention and the commercial performance of Zytiga®. Instead, any commercial success of Zytiga® is likely due to the effectiveness of abiraterone acetate in treating prostate cancer.

In particular, Applicants presented *no* evidence to suggest that the claimed invention, rather than the prior art abiraterone acetate, was responsible for any commercial success of Zytiga.® Instead, Applicants mislead the Examiner by arguing that because Zytiga® is approved in combination with prednisone, Zytiga® is a commercial embodiment of the claimed invention. AMG Ex. 1012 at p. 7. Applicants then extrapolated that the sales of Zytiga® were evidence of the commercial success of the invention. However, this is incorrect as a matter of law because Zytiga® is the trade name under which abiraterone acetate is marketed.

And abiraterone acetate by itself is *not* a commercial embodiment of the claimed invention.

Specifically, the active ingredient in Zytiga® is abiraterone acetate.

Abiraterone acetate and its use in treating prostate cancer are claimed in the '213 patent. Therefore, Zytiga® is a commercial embodiment of the '213 patent, not the '438 patent. In order to overcome the Examiner's *prima facie* case of obviousness by arguing commercial success, Applicants were required to provide sufficient evidence of a nexus between the commercial performance of Zytiga® and any incremental clinically significant anti-cancer benefit of administering the combination of abiraterone acetate and prednisone over abiraterone alone. Applicants provided no such evidence. Having failed to do so, Applicants failed to meet their burden of proof.

B. One of Skill Would Not Anticipate Unexpected Benefits from the Claimed Invention and Applicants Did Not Offer Any Evidence of Relevant Unexpected Results

Although Zytiga® is approved in combination with prednisone, as Dr. Serels explains, the anti-cancer effect of administering Zytiga® to treat prostate cancer is obtained from abiraterone acetate. AMG Ex. 1002, Serels Decl. at ¶84. This is because the prednisone administered with abiraterone in accordance with the approved indication for Zytiga® is intended as *hormone replacement therapy*

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related to administration of a CYP17 inhibitor, and not as an *anti-cancer therapy*.

AMG Ex. 1002, Serels Decl. at ¶¶68-70, 74-78. Therefore, one of skill would not expect the administration of the combination of abiraterone acetate and prednisone to provide any additional clinically significant anti-cancer benefit in treating prostate cancer beyond the anti-cancer benefit obtained from the administration of abiraterone acetate alone. AMG Ex. 1002, Serels Decl. at ¶¶74, 80.

Importantly, abiraterone acetate was known as an anti-cancer agent at least as of the earliest priority date of the claimed invention. In particular, abiraterone acetate was known as an anti-cancer agent for the treatment of prostate cancer. AMG Ex. 1002, Serels Decl. at ¶¶36, 45. For example, abiraterone acetate for the treatment of prostate cancer was disclosed and claimed in the '213 patent. AMG Ex. 1002, Serels Decl. at ¶¶36, 45, 73. Abiraterone acetate had been shown to reduce testosterone levels in refractory metastatic prostate cancer patients in clinical trials. AMG Ex. 1002, Serels Decl. at ¶¶36, 45. Therefore, the proper comparison for overcoming obviousness over the prior art based on unexpected results should have been whether there was any unexpected synergistic *anti-cancer* benefit of using the *combination of abiraterone and prednisone* beyond the anti-cancer effect of *abiraterone alone*.

But Applicants never once argued unexpected results of administering abiraterone and prednisone over abiraterone alone. Instead, Applicants mislead the

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Examiner by arguing alleged unexpected benefits of abiraterone and prednisone over prednisone and a placebo. *See e.g.*, July 3, 2012 Response (AMG Ex. 1008), January 11, 2013 Response (AMG Ex. 1010); June 4, 2013 Response (AMG Ex. 1012). However, evidence of any purported benefits of abiraterone and prednisone over prednisone and a placebo is insufficient as a matter of law to overcome a *prima facie* case of obviousness over the closest prior art, *i.e.*, abiraterone.

Tellingly, the assignee of the '438 patent and NDA holder, Janssen Biotech Inc., has never described the co-administration of prednisone with Zytiga® as enhancing the anti-cancer activity of Zytiga® in information provided to healthcare practitioners. AMG Ex. 1002, Serels Decl. at ¶¶75-78. Instead, in prescribing information for Zytiga®, including the 2011 Approval Prescribing Information; and the 2015 revised Prescribing Information and accompanying brochure on co-administration, it is explained that co-administration of prednisone with Zytiga® is intended to reduce adverse effects, such as hypertension, hypokalemia and fluid retention that may result from CYP17 inhibition of cortisol production and consequent ACTH drive. AMG Ex. 1018, 2011 Zytiga® Approval Prescribing Information, at pp. 3-4, 5-6, 11; AMG Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at pp. 2-3.

For example, the 2015 brochure "Putting Prednisone in Perspective," that accompanies the 2015 revised Prescribing Information for Zytiga®, states that

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"prednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with Zytiga®" and that "coadministration [sic] of prednisone [with Zytiga®] suppresses the ACTH drive and reduces the incidence and severity of mineralocorticoid excess adverse reactions." AMG Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at p. 2.

Indeed, the Zytiga® 2015 Prescribing Information makes clear that prednisone is co-administered as hormone replacement therapy and that "7.5 mg/day to 10 mg/day of prednisone is approximately the physiologic equivalent of the amount of endogenous cortisol normally produced on a daily basis." AMG Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at p. 3.

As Dr. Serels explains in his accompanying declaration, it was known in the art that administering ketoconazole, also a CYP17 inhibitor like abiraterone acetate, to treat a prostate cancer may result in significant side effects, such as hypertension, hypokalemia and fluid retention as a result of a decrease in cortisol levels and consequent ACTH drive. AMG Ex. 1002, Serels Decl. at ¶¶34, 68-70. These adverse effects reduced the safety of administering ketoconazole as a single agent. AMG Ex. 1002, Serels Decl. at ¶¶34, 68-70. Therefore, it was common practice in the art to co-administer a glucocorticoid as replacement therapy when administering ketoconazole to treat prostate cancer in a human patient in order to improve the safety and enhance the tolerability of treatment. AMG Ex. 1002,

Serels Decl. at ¶¶35, 68-70. The particular combination of ketoconazole and prednisone was known to be safe and effective in treating patients with metastatic refractory prostate cancer based on at least the teachings of Gerber. *See, e.g.*, Exhibit 1004, Gerber, *Abstract*; AMG Ex. 1002, Serels Decl. at ¶¶48-49, 68-70.

Based on at least these teachings, one of skill in the art would have had a reasonable expectation that administration of abiraterone, a more selective CYP17 inhibitor than ketoconazole, to treat a patient with prostate cancer would require the co-administration of a glucocorticoid such as prednisone in order to improve safety and enhance tolerability of administration. AMG Ex. 1002, Serels Decl. at ¶¶48-49, 68-70.

To the extent that the co-administration of prednisone with abiraterone made treatment of prostate cancer with abiraterone safer and/or more tolerable, this greater safety and/or tolerability was expected, based on the teachings of the prior art, including Gerber. *See, e.g.*, AMG Ex. 1004, Gerber, *Abstract*, pp. 1178-1179; AMG Ex. 1020, Harris, p. 544; AMG Ex. 1021, Oh, *Abstract*, p. 90; AMG Ex. 1003, O'Donnell, p. 2323; AMG Ex. 1002, Serels Decl. at ¶¶68-70, 74, 80.

C. The '438 Patent Satisfied No Long-Felt But Unmet Need

Patentees may argue that commercial performance of Zytiga® is evidence of long-felt but unmet need. However, as explained by Dr. McDuff, any success of Zytiga® that is not a result of the claimed invention is irrelevant to secondary

considerations. AMG Ex. 1017, McDuff Decl. at ¶¶31-35. As Dr. Serels explains, the combination of abiraterone acetate and prednisone does not produce unexpected results in anti-cancer benefit. AMG Ex. 1002, Serels Decl. at ¶¶74, 80, 83. In fact, the perception among clinicians is that the requirement to co-administer prednisone with Zytiga is a drawback to its use to treat prostate cancer. AMG Ex. 1002, Serels Decl. at ¶85. For at least these reasons, the combination of abiraterone and prednisone satisfied no long-felt need beyond what abiraterone may have done.

D. The '213 is a Blocking Patent that Limits the Applicability of Commercial Success

The Federal Circuit has held that the existence of a blocking patent limits the applicability of any evidence of commercial success to overcome a *prima facie* case of obviousness. *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376–77 (Fed. Cir. 2005) (where "market entry by others was precluded" as a result of a patent covering the active ingredient and its method of use and FDA exclusivity, "the inference of non-obviousness of weekly-dosing, from evidence of commercial success, is weak."). Both abiraterone acetate and its use for the treatment of prostate cancer are claimed in the '213 patent. AMG Ex. 1002, Serels Decl. ¶¶36, 45, 73. The FDA's Orange Book lists the '213 patent as

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covering Zytiga®¹. Because the '213 patent claims abiraterone acetate and its use in a method of treating an androgen-dependent disorder, “no entity other than” the patentee “could have successfully brought [abiraterone acetate] to market.”

Galderma Labs. v. Tolmar, Inc., 737 F.3d 731, 740-41 (Fed. Cir. 2013). The ability of the patentees of the '213 to block additional research and development of abiraterone acetate limits the relevance of commercial success for the '438 patent. AMG Ex. 1017, McDuff Decl. at ¶¶18-20.

As Dr. McDuff explains, from an economic perspective, commercial success presumes that if an idea were obvious to market participants, then others would have brought that idea to market sooner had there been economic incentives to do so. AMG Ex. 1017, McDuff Decl. at ¶¶16-17. A finding of commercial success can, in some circumstances, support the notion that a patent was not obvious to those skilled in the art if those incentives for development existed. AMG Ex. 1017, McDuff Decl. at ¶¶17. However, in this case, the '213 patent was a blocking patent that limited economic incentives to develop the invention of the '438 patent. AMG Ex. 1017, McDuff Decl. at ¶¶18-20. As Dr. McDuff explains, “Because Johnson & Johnson could have effectively prevented market participants from

¹ FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed 07/24/2015).

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supplying an abiraterone product, typical incentives associated with drug development would not have existed." AMG Ex. 1017, McDuff Decl. at ¶20.

E. Copying By Generic Drug Makers Is Irrelevant

Finally, the Patentees may argue that Petitioners and other generic drug companies seek to copy the invention of the '438 Patent by commercializing generic versions of abiraterone acetate. Because copying "is required for FDA approval" of generic drugs, any "evidence of copying in the [generic drug] context is not probative of nonobviousness." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

XIV. CONCLUSION

For the reasons discussed above, Petitioners request that the Board institute an *inter partes* review and determine that all claims (1-20) of the '438 patent be canceled as unpatentable.

Respectfully submitted,

/William D. Hare/

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Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on December 4, 2015, I caused to be served true and correct copies of the foregoing:

- PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,822,438
- Exhibits 1001-1067
- Power of Attorney

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EXHIBIT E

Filed: June 30, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner

v.

JANSSEN ONCOLOGY, INC.,

Patent Owner

U.S. Patent No. 8,822,438 to Auerbach et al.

Inter Partes Review IPR2016-01332

Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438

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LISTING OF EXHIBITS

Exhibit	Description
MYL 1001	U.S. Patent No. 8,822,438, Auerbach and Beldegrun, “Methods and Compositions for Treating Cancer” (“the ’438 patent”)
MYL 1002	Declaration of Marc B. Garnick, MD (“Garnick Decl.”)
MYL 1003	O’Donnell, A. et al., “Hormonal impact of the 17 α -hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer,” Br. J. Cancer, (90):2317–2325 (2004) (“O’Donnell”)
MYL 1004	Gerber, G.S. et al., “Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic cancer,” J. Urology, 144(5):1177–9 (1990) (“Gerber”)
MYL 1005	U.S. Patent No. 5,604,213, Barrie S.E. et al., “17-Substituted Steroids Useful In Cancer Treatment” (“the ’213 patent”)
MYL 1006	Tannock, I. et al., “Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points,” J. Clinical Oncology, 14:1756–1764 (1996) (“Tannock”)
MYL 1007	February 3, 2012 Office Action (excerpt from prosecution history of ’438 patent)
MYL 1008	July 3, 2012 Response (excerpt from prosecution history of ’438 patent)
MYL 1009	Ryan, C.J. et al., “Abiraterone in metastatic prostate cancer without previous chemotherapy,” New Eng. J. Med., 368:138–148 (2013).
MYL 1010	January 11, 2013 Response (excerpt from prosecution history of ’438 patent)
MYL 1011	March 4, 2013 Office Action (excerpt from prosecution history of ’438 patent)
MYL 1012	June 4, 2013 Response (excerpt from prosecution history of ’438 patent)

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MYL 1013	July 3, 2013 Notice of Allowance (excerpt from prosecution history of '438 patent)
MYL 1014	October 25, 2013 Notice of Allowance (excerpt from prosecution history of '438 patent)
MYL 1015	February 11, 2014 Notice of Allowance (excerpt from prosecution history of '438 patent)
MYL 1016	June 2, 2014 Notice of Allowance (excerpt from prosecution history of '438 patent)
MYL 1017	Declaration of Ivan T. Hofmann ("Hofmann Declaration")
MYL 1018	2011 Zytiga® Approval Prescribing Information
MYL 1019	2015 Zytiga® Prescribing Information, Co-administration Brochure
MYL 1020	Harris, K.A. et al., "Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer," J. Urology, 168:542–545 (August 2002)
MYL 1021	Oh, W.K. "Secondary hormonal therapies in the treatment of prostate cancer," Urology, 60(Supp. 3A):87–93 (2002)
MYL 1022	Tannock, I. et al., "Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer," N. Eng. J. Med., 351:1502–12 (2004)
MYL 1023	Attard, G. et al., "Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer," Br. J. Urol. 96(9): 1241–1246 (2005)
MYL 1024	Hellerstedt, B.A. et al., "The current state of hormonal therapy for prostate cancer," CA Cancer J. Clin., 52:154–179 (2002).
MYL 1025	Kasper, D.L. et al. (Eds.), Harrison's Principles of Internal Medicine, 16th Edition (2005), 549.

Exhibit	Description
MYL 1026	Auchus, R.J. “The genetics, pathophysiology, and management of human deficiencies of P450c17,” Endocrinol. Metab. Clin. North Am. 30(1):101–119 (2001)
MYL 1027	Costa-Santos, M. et al., “Two prevalent CYP17 mutations and genotype-phenotype correlations in 24 Brazilian patients with 17-hydroxylase deficiency,” J. Clin. Endocrin. & Metabol. 89(1):49–60 (2004)
MYL 1028	Jubelirer, S.J., et al., “High dose ketoconazole for the treatment of hormone refractory metastatic prostate carcinoma,” J. Urol., 142(1):89–91 (1989)
MYL 1029	U.S. Patent 5,688,977, Sisti, N.J. et al., “Method for Docetaxel Synthesis”
MYL 1030	U.S. Food and Drug Administration (“FDA”) FDA News Release dated May 19, 2004, “FDA Approves New Indication for Taxotere-Prostate Cancer”
MYL 1031	Tannock, I. et al., “Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response,” J. Clin. Oncology, 7:590–7 (1989)
MYL 1032	Intentionally left blank
MYL 1033	Scher, H.I. et al., “Increased survival with enzalutamide in prostate cancer after chemotherapy,” New Eng. J. Med., 367:1187–97 (2012)
MYL 1034	de Bono, J.S. et al., “Abiraterone and increased survival in metastatic prostate cancer,” New Engl. J. Med., 364:1995–2005 (2011)
MYL 1035	Orange Book listing for Zytiga®
MYL 1036	Initial Application (excerpt from prosecution history of ’438 patent)
MYL 1037	Intentionally left blank
MYL 1038	Intentionally left blank

Exhibit	Description
MYL 1039	September 11, 2012 Office Action (excerpt from prosecution history of '438 patent)
MYL 1040	Cancer.net (ASCO Patient Website), Treatment of Metastatic Castration-Resistant Prostate Cancer, http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer (accessed 6/28/2016).
MYL 1041	Cancer.org (ACS), "What are the key statistics about prostate cancer?" http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics (accessed 6/28/2016).
MYL 1042	Intentionally left blank
MYL 1043	Intentionally left blank
MYL 1044	Intentionally left blank
MYL 1045	FDA News Release, "FDA expands Zytiga's use for late-stage prostate cancer," 12/10/2012 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm (access 6/30/2016).
MYL 1046	FDA Website, Drugs@FDA – Zytiga, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed 6/28/2016).
MYL 1047	FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed 6/30/2016).
MYL 1048	<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731, 740–41 (Fed. Cir. 2013).
MYL 1049	Jevtana Website, Dosing and Administration, http://www.jevtana.com/hcp/dosing/default.aspx (accessed 6/28/2016).

Exhibit	Description
MYL 1050	Kirby, M. et al., “Characterising the castration-resistant prostate cancer population: A systematic review,” <i>Int’l J. Clinical Practice</i> 65(11):1180–1192 (2011).
MYL 1051	Mayo Clinic Website, Prostate cancer, http://www.mayoclinic.org/diseasesconditions/prostate-cancer/basics/definition/con-20029597?p=1 (accessed 6/28/2016).
MYL 1052	Intentionally left blank
MYL 1053	<i>Merck & Co. v. Teva Pharms. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005).
MYL 1054	Murphy, W.J., J.L. Orcutt & P.C. Remus (2012), <i>Patent Valuation: Improving Decision Making through Analysis</i> , Hoboken, NJ: Wiley.
MYL 1055	PMLiVe Website, “Top 50 Pharmaceutical Products by Global Sales,” http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales (accessed 6/30/2016).
MYL 1056	Intentionally left blank
MYL 1057	<i>Syntex (U.S.A.) LLC v. Apotex, Inc.</i> , 407 F.3d 1371 (Fed. Cir. 2005).
MYL 1058- MYL 1063	Intentionally left blank
MYL 1064	Zytiga Brochure, Putting Prednisone in Perspective, 3/2015.
MYL 1065	Zytiga Label, 5/20/2015.
MYL 1066	Zytiga Website, How Zytiga® (abiraterone acetate) Works, https://www.zytiga.com/print/about-zytiga/how-zytiga-works (accessed 6/28/2016).
MYL 1067	Intentionally left blank
MYL 1068	November 25, 2011 Office Action (excerpt from prosecution history of ’438 patent)
MYL 1069	December 21, 2011 Response (excerpt from prosecution history of ’438 patent)

Exhibit	Description
MYL 1070	September 11, 2012 Office Action (excerpt from prosecution history of '438 patent)
MYL 1071	October 3, 2013 IDS (excerpt from prosecution history of '438 patent)
MYL 1072	October 3, 2013 IDS (excerpt from prosecution history of '438 patent)
MYL 1073	January 10, 2014 IDS (excerpt from prosecution history of '438 patent)
MYL 1074	May 9, 2014 IDS (excerpt from prosecution history of '438 patent)
MYL 1075	May 9, 2014 IDS (excerpt from prosecution history of '438 patent)
MYL 1076	May 30, 2014 IDS (excerpt from prosecution history of '438 patent)
MYL 1077	May 30, 2014 IDS (excerpt from prosecution history of '438 patent)
MYL 1078	Barrie et al., "Pharmacology of novel steroidal inhibitors of Cytochrome P450 _{17α} (17 α -hydroxylase/C17,20 lyase)," J. Steroid Biochem. Molec. Biol. 50:267-73 (1994)
MYL 1079	Fakih, M. et al., "Glucocorticoids and treatment of prostate cancer: A preclinical and clinical review," Urology 60:553-561 (2002)
MYL 1080	Lam, J.S. et al., "Secondary hormonal therapy for advanced prostate cancer," J. Urology 175:28-34 (2006)

TABLE OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotrophic hormone
AR	Androgen receptor
CRPC	Castration-resistant prostate cancer
mCRPC	Metastatic castration-resistant prostate cancer
CYP17	17 α -hydroxylase/C17,20-lyase
DHT	Dihydrotestosterone
IDS	Information Disclosure Statement
LH	Luteinizing hormone
NDA	New Drug Application
POSA	Person of Ordinary Skill in the Art
PSA	Prostate-specific antigen
RCE	Request for Continued Examination

I. INTRODUCTION

Mylan Pharmaceuticals Inc. (“Petitioner”) petitions for *Inter Partes* Review of claims 1-20 of U.S. Patent No. 8,822,438 to Auerbach *et al.* (“the ’438 patent”) (MYL Ex. 1001), which is assigned to Janssen Oncology, Inc. (“Janssen”), under 35 U.S.C. §§ 311–319 and 37 C.F.R. Part 42 and seeks a determination that all claims (1-20) of the ’438 patent be canceled as unpatentable.

This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith is a power of attorney and an exhibit list per § 42.10(b) and § 42.63(e), respectively. Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this Petition.

II. MANDATORY NOTICES

Petitioner provides the following mandatory notices.

A. Real Parties-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The real parties-in-interest for Petitioner are Mylan Pharmaceuticals Inc., Mylan Inc., Mylan N.V., and Mylan LLC.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

The following litigations or instituted *inter partes* reviews related to the ’438 patent are pending:

- *Amerigen Pharms. Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286 (P.T.A.B.);

- *Argentum Pharms. LLC v. Janssen Oncology, Inc.*, IPR2016-01317 (P.T.A.B.).
- *BTG Int'l Ltd. v. Actavis Labs. FL, Inc.*, No. 15-cv-5909-KM-JBC (D.N.J.);
- *BTG Int'l Ltd. v. Amerigen Pharms., Inc.*, No. 16-cv-02449-KM-JBC (D.N.J.);
- *BTG Int'l Ltd. v. Glenmark Pharms. Inc., USA*, No. 16-cv-03743-KM-JBC (D.N.J.); and
- *Janssen Biotech, Inc. v. Mylan Pharms. Inc.*, No. 15-cv-00130-IMK (N.D.W. Va.).

C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioner consents to electronic service by e-mail at

the above listed email addresses of lead and back-up counsel (bmwhite@perkinscoie.com and bbeel@perkinscoie.com).

III. GROUNDS FOR STANDING (37 C.F.R. §§ 42.101 and 42.104)

As required by 37 C.F.R. § 42.104(a), Petitioner certifies that the '438 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified herein.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.22(a) and 37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review and cancellation of claims 1–20. Petitioner's full statement of the reasons for the relief requested is set forth below.

Petitioner respectfully requests *inter partes* review and cancellation of claims 1–20 of the '438 Patent based on the grounds set forth below:¹

Ground 1: Claims 1-20 are unpatentable as obvious under 35 U.S.C. § 103 over O'Donnell in view of Gerber

Ground 2: Claims 1-4 and 5-11 are unpatentable as obvious under 35 U.S.C. § 103 over the '213 patent in view of Gerber.

In support of these grounds for unpatentability, Petitioner submits the expert declaration of Marc B. Garnick, M.D. (MYL Ex. 1002 ("Garnick Decl.")) and the

¹ Mylan's asserted grounds of obviousness are the same as those instituted in

IPR2016-00286, filed by Amerigen Pharmaceuticals Limited.

declaration of economics expert Ivan T. Hofmann (MYL Ex. 1017 (“Hofmann Decl.”)). Petitioner also relies on the other Exhibits set forth in the concurrently filed Listing of Exhibits.

V. THRESHOLD REQUIREMENT FOR INTER PARTES REVIEW

A petition for *inter partes* review must demonstrate “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). This Petition meets this threshold. As explained below, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

The claims of the ’438 patent are directed to treating prostate cancer by administering therapeutically effective amounts of abiraterone acetate, a 17 α -hydroxylase/C17,20-lyase inhibitor (“CYP17 inhibitor”), in combination with prednisone, a glucocorticoid. MYL Ex. 1002, Garnick Decl. ¶¶34–35. The prior art taught the use of abiraterone acetate as an effective anti-cancer agent that suppresses testosterone synthesis in prostate cancer patients. MYL Ex. 1002, Garnick Decl. ¶¶36, 55, 66, 68. It was known as of the earliest priority date claimed by the ’438 patent that testosterone promoted prostate cancer proliferation and progress, so that testosterone synthesis must be suppressed to treat prostate cancer.

However, it was also known that in using a CYP17 inhibitor to reduce testosterone synthesis, the CYP17 inhibitor undesirably suppressed the production of cortisol, a glucocorticoid, which is necessary for other biochemical cycles in the body. In particular, reduced production of cortisol caused adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. To address the suppressed synthesis of cortisol, the prior art taught that concomitant glucocorticoid replacement therapy might be necessary when administering abiraterone to treat prostate cancer in a patient, and that this was common practice in the treatment of prostate cancer with ketoconazole, another CYP17 inhibitor. MYL Ex. 1002, Garnick Decl. ¶¶42, 44, 58.

The prior art also taught that abiraterone was a more effective CYP17 inhibitor than ketoconazole. For example, the prior art taught that abiraterone acetate was more effective in decreasing testosterone levels in a mammal than ketoconazole. MYL Ex. 1002, Garnick Decl. ¶¶46, 55. The prior art also taught that the combination of ketoconazole and prednisone was a safe and effective treatment for refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶58.

One of skill in the art would have combined abiraterone acetate and prednisone based on the teachings of O'Donnell in view of Gerber, and/or the '213 patent in view of Gerber, for a safe and effective treatment of prostate cancer with

a reasonable expectation of success. The prior art taught that abiraterone acetate was a more effective CYP17 inhibitor than ketoconazole and that the combination of ketoconazole and prednisone was safe and effective to treat patients with hormone refractory metastatic prostate cancer, which would have motivated the combination. MYL Ex. 1002, Garnick Decl. ¶¶55–59. One of skill in the art may also have been motivated by prednisone’s possible anti-cancer effects. *Id.* ¶ 89.

There are no secondary considerations of commercial success that overcome this case of obviousness. The claims of the application that resulted in the ’438 patent were repeatedly rejected for obviousness until the Examiner allowed the claims based on the purported “unexpected commercial success” of Zytiga, the brand name under which abiraterone acetate is marketed in the United States by the Assignee. In particular, the Examiner’s allowance of the claims based on secondary considerations of commercial success of Zytiga was in error because Applicants failed to show the necessary nexus between the claimed invention (which is directed to a method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga.

B. Level of Ordinary Skill in the Art

A person of ordinary skill in the art is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary

creativity. With respect to the '438 patent, the scientific field relevant is oncology or urology. MYL Ex. 1002, Garnick Decl. ¶18. A person of ordinary skill in the art would be a physician specializing in urology, endocrinology, or oncology, or a person holding a Ph.D. in pharmacology, biochemistry or a related discipline, such as pharmaceutical science. MYL Ex. 1002, Garnick Decl. ¶18. Additional experience could substitute for the advanced degree. MYL Ex. 1002, Garnick Decl. ¶18. To the extent necessary, one of skill in the art may collaborate with one or more other persons of skill in the art for one or more aspects with which the other person may have expertise, experience and/or knowledge that was obtained through his or her education, industrial or academic experiences. MYL Ex. 1002, Garnick Decl. ¶19. For example, one of skill may consult with an endocrinologist, oncologist, or medical biochemist and thus may rely on the opinions of such specialists in evaluating the claims. MYL Ex. 1002, Garnick Decl. ¶20.

C. U.S. Patent No. 8,822,438 and Its File History

1. Specification of the '438 Patent

The “Background” section of the '438 patent describes prostatectomy and radiotherapy, a primary course of treatment for patients diagnosed with organ-confined prostate cancer, as being highly invasive and ineffective on metastasized prostate cancer. MYL Ex. 1001, col. 1, ll. 25–32. In addition, the specification states that these localized treatments are not effective on prostate cancer after it has

metastasized and that, moreover, a large percent of individuals who receive such localized treatments will suffer from “recurring cancer.” *Id.* at ll. 28–33. The specification states that another treatment option for prostate cancer, hormone therapy, is less invasive than surgery and has fewer side effects. *Id.* at ll. 43–44, 51–53. However, the specification notes that hormone therapy is not equally effective in all patients thus treated, and some patients suffer from relapsing or recurring cancer after hormone therapy. *Id.* at ll. 57–64.

The “Summary of the Invention” section of the ’438 patent describes various embodiments of the invention as being directed to methods and compositions of treating a refractory cancer in a patient, involving administering an effective amount of a CYP17 inhibitor and an effective amount of another anticancer agent such as mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including prednisone or dexamethasone. MYL Ex. 1001, col. 2, l. 9 – col. 3, l. 20.

The “Definitions” section defines “17 α -hydroxylase/C17,20-lyase inhibitor” as an inhibitor of the enzyme “17 α -hydroxylase/C17,20-lyase” (an enzyme involved in testosterone synthesis). MYL Ex. 1001, col. 3, l. 66 – col. 4, l. 7. The terms “treat,” “treating” and “treatment” are defined as “includ[ing] the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the

spread of cancer.” MYL Ex. 1001, col. 3, ll. 46–50. The term “anti-cancer agent” is defined as “any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells.” MYL Ex. 1001, col. 4, ll. 8–16. The term “refractory cancer” is defined as “cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment.” MYL Ex. 1001, col. 4, ll. 23–27.

The “Detailed Description of the Invention” section refers to U.S. Patent No. 5,604,213 (MYL Ex. 1005) for its disclosure of CYP17 inhibitors being “shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer.” MYL Ex. 1001, col. 5, ll. 23–29. The specification provides a list of various CYP17 inhibitors including abiraterone (17-(3-pyridyl)-androsta-5,16-diene-3 β -ol). MYL Ex. 1001, col. 5, ll. 30–40.

According to the specification, the CYP17 inhibitors may also be administered or combined with steroids, such as corticosteroids or glucocorticoids including hydrocortisone, prednisone, or dexamethasone, in the same or different compositions. MYL Ex. 1001, col. 10, ll. 15–21. A single-unit solid oral dosage form may contain about 50 mg to about 300 mg of abiraterone acetate and about 0.5 to 3 mg of a steroid, *e.g.*, glucocorticoid, optionally with additional excipients. MYL Ex. 1001, col. 10, ll. 42–50. Suitable daily dosages of CYP17 inhibitors

according to the '438 patent can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day. MYL Ex. 1001, col. 11, ll. 33–43.

According to the specification, the method for the treatment of cancer can comprise administering an amount of about 50 mg/day to about 2000 mg/day or about 500 mg/day to about 1500 mg/day of abiraterone acetate, and an amount of about 0.01 mg/day to about 500 mg/day or about 0.5 mg/day to about 25 mg/day of glucocorticoid, such as hydrocortisone, dexamethasone or prednisone. MYL Ex. 1001, col. 13, ll. 6–39.

One example of a composition according to the invention comprises a CYP17 inhibitor such as abiraterone acetate in combination with a steroid, such as hydrocortisone, prednisone or dexamethasone. The composition can comprise about 50–500 mg of abiraterone acetate, and about 0.25–3.5 mg of steroid. MYL Ex. 1001, col. 15, ll. 52–55.

2. File History of the '438 Patent

The '438 patent has a lengthy and involved prosecution. The application resulting in the '438 Patent was filed on February 24, 2011, and assigned Application No. 13/034,340. MYL Ex. 1001, cover page ¶¶(21), (22). The application was filed as a continuation of Application No. 11/844,440, filed on August 24, 2007, which claims priority to Provisional Application No. 60/921,506, filed on August 25, 2006. *Id.* ¶¶(60), (63).

In an Office Action dated November 25, 2011, the Examiner imposed restriction between the claims of Group I (claims 1–26, drawn to a method for treating cancer), and the claims of Group II (claims 27–36, drawn to a composition). MYL Ex. 1068, November 25, 2011, Office Action at 2. In a Response dated December 21, 2011, Applicants cancelled the pending claims, and elected the invention of Group I, represented by newly-presented claims 37–56. MYL Ex. 1069, December 21, 2011, Response at 1–5. Newly-presented claims 37–56 are substantively similar to claims 1–20 of the '438 patent as issued.

In an Office Action dated February 3, 2012, all pending claims (*i.e.*, 37–56) were rejected for obviousness over O'Donnell (MYL Ex. 1003) in view of Tannock (MYL Ex. 1006). MYL Ex. 1007, February 3, 2012 Office Action, at 2. The Examiner characterized O'Donnell as disclosing the CYP17 inhibitor abiraterone acetate being used to suppress testosterone levels in prostate cancer patients. *Id.* Tannock was cited for teaching “10 mg of prednisone in combination with other anit-cancer [*sic*] drug [*i.e.*, mitoxantrone] as effective in treating refractory hormonal-resistance [*sic*] prostate cancer.” MYL Ex. 1007 at 3.

In a Response dated July 3, 2012, Applicants argued that “[n]othing in the art teaches or suggests that abiraterone acetate in combination with prednisone would be a particularly useful combination for cancer treatment.” July 3, 2012 Response (MYL Ex. 1008) at 2. Applicants further argued that “[e]ven if one of

ordinary skill would have been motivated to combine both modes of treatment, the claimed invention produces unexpected results.” *Id.*

As alleged evidence in support of unexpected results, Applicants cited Sartor, *Nature Reviews Clinical Oncology*, 8:515–516 (2011), reporting data from a clinical study of patients with metastatic castration-resistant prostate cancer (“mCRPC”) previously treated with chemotherapy who were treated with the combination of abiraterone and prednisone or prednisone alone. *Id.* Applicants described Sartor as teaching that “[a]biraterone plus prednisone prolongs overall survival relative to prednisone alone.” MYL Ex. 1008 at 2.

Applicants also argued that worldwide sales data for Zytiga (the trade name under which abiraterone acetate is marketed) were evidence of purported commercial success of the claimed invention. *Id.* at 3. According to the Applicants, sales of Zytiga were evidence of the commercial success of the claimed combination because the approved label for Zytiga directs patients to use Zytiga in combination with prednisone. *Id.*

In a Final Office Action dated September 11, 2012, the Examiner maintained the rejection of the claims over O’Donnell and Tannock. MYL Ex. 1070, September 11, 2012, Office Action at 2–4. In a Request for Continued Examination (“RCE”) and Response dated January 11, 2013, Applicants once again argued unexpected results and cited Ryan *et al.*, *New Eng. J. of Med.*,

368:138–148 (2013) (MYL Ex. 1009), purporting to show unexpected results of the claimed invention over prednisone. MYL Ex. 1010 at 6. For example, Applicants argued an “unexpected survival benefit of abiraterone in combination with prednisone” over “prednisone alone.” MYL Ex. 1010, January 11, 2013 Response at 7; MYL Ex. 1002, Garnick Decl. ¶77.

In a Final Office Action dated March 4, 2013, the Examiner continued to maintain the obviousness rejection of claims 37–56 over O’Donnell and Tannock. MYL Ex. 1011, March 4, 2013 Office Action at 2. The Examiner explained that “[s]ince abiraterone acetate provide a new mechanism of action in treating prostate cancer and prednisone is known to be useful in treating refractory prostate cancer, concomitant employment of both compounds into a single method useful for the very same purpose, treating prostate cancer, would be considered *prima facie* obvious.” *Id.*

However, as explained in the Garnick Declaration, the Examiner’s stated reasons for combining both compounds into a single method included incorrect facts. First, abiraterone acetate did not provide a new mechanism of action. As explained above and set out in O’Donnell, both ketoconazole and abiraterone were known CYP17 inhibitors acting by the same mechanism. MYL Ex. 1002 (Garnick Declaration) ¶¶33, 36. Second, prednisone was not accepted as being useful for treating cancer. As explained in the Garnick Declaration, MYL Ex. 1002, Garnick

Decl. ¶¶83-84, 89, 90, although there was a belief that prednisone might be useful for treating prostate cancer, at the time of filing of the '438 patent, prednisone's use as an effective anti-cancer agent for prostate cancer was much less clear than its use as a palliative agent. It was therefore common practice to co-administer a glucocorticoid such as prednisone with a CYP17 inhibitor for glucocorticoid replacement. MYL Ex. 1002, Garnick Decl. ¶¶44, 58, 78.

In a Notice of Appeal and Response dated June 4, 2013, Applicants reiterated their argument that Tannock purportedly taught away from the use of prednisone with abiraterone acetate because Tannock taught that “[t]here was no significant difference in overall survival [between prednisone alone and prednisone plus the anti-cancer agent mitoxantrone].” Response dated June 4, 2013 (MYL Ex. 1012) at 6 (brackets in original). Applicants argued that one of skill in the art, reading Tannock, would have expected “there to be no difference in survival between one cancer agent alone, and that same cancer agent in combination with prednisone.” MYL Ex. 1012 at 6.

Applicants also provided the FDA approval label for Zytiga and argued that “[t]aking Zytiga in accordance with the approved label [*i.e.*, in combination with prednisone] represents a commercial embodiment of the presently claimed invention.” MYL Ex. 1012 at 7. Applicants also submitted a news release from FDA announcing that Zytiga was approved for the additional indication “for use in

prostate cancer patients prior to receiving chemotherapy” and argued that this provided additional evidence of commercial success of the claimed combination. MYL Ex. 1012 at 7.

Applicants once again argued commercial success, this time based on market share data for Zytiga, and a Janssen-created presentation entitled “Pharmaceuticals Commercial Overview” by Joaquin Duato, Worldwide Chairman, Pharmaceuticals, Janssen, dated May 2013 (“Duato presentation”), which characterized Zytiga as having the most successful launch of an oral oncology product ever: “Zytiga[®]: Most Successful Oral Oncology Launch in History.” MYL Ex. 1012 at 7; *id.* at Exhibit page 40 (slide 11).

Applicants specifically pointed to a slide showing a 70% market share for Zytiga in July 2012 for “chemo refractory prostate cancer patients.” MYL Ex. 1012 at 7. Applicants argued that the Duato presentation showed that “[d]espite another product, Xtandi, being introduced in August of 2012, by April of 2013, Zytiga was still the market leader as of April 2013 with 57% market share in chemorefractory prostate cancer patients.” MYL Ex. 1012 at 7-8. Applicants concluded that “not only is ZYTIGA the most successful oral oncology launch in history, two years after its initial approval it is still the market leader for chemo refractory patients despite an earlier introduced therapy [*i.e.*, Jevtana[®]] and a later introduced therapy [*i.e.*, Xtandi[®]].” MYL Ex. 1012 at 8. Applicants argued that

“[t]his commercial success [of Zytiga] demonstrates the non-obviousness of the presently claimed invention.” MYL Ex. 1012 at 8.

In a Notice of Allowability dated July 3, 2013, all pending claims were allowed with the Examiner providing the following reason for allowance: “The *unexpected commercial success* of the launch of the drug obviates the rejection under 35 USC 103(a).” MYL Ex. 1013, Notice of Allowability dated July 3, 2013 at 2 (emphasis added).

In a pair of Information Disclosure Statements (“IDS”) dated October 3, 2013, submitted with an RCE, Applicants provided a number of non-patent literature documents.² MYL Exs. 1071-72. Among the references listed in the October 3, 2013 IDS was Gerber (MYL Ex. 1004). MYL Ex. 1071 at 3 (Item No. 17). A second Notice of Allowability issued October 25, 2013, with the Examiner stating in the Notice that the reasons for allowance were “essentially the same” as in the previous notice. MYL Ex. 1014 at 2.

Another IDS submitted with a second RCE and listing additional non-patent documents was filed by Applicants on January 10, 2014. MYL Ex. 1073. A third

² In all, in the ten months *after* receiving their first Notice of Allowability for the ’438 patent, the Applicants submitted seven Information Disclosure Statements to the Patent Office listing 95 newly-cited references. Applicants did not submit any Information Disclosure Statements before allowance.

Notice of Allowability issued on February 11, 2014. MYL Ex. 1015. The Examiner again stated in the Notice of Allowability that the reasons for allowance were “essentially the same as the notice of allowance mailed 7/30/2013,” and further that “[t]he commercial success of the combination of prednisone and abiraterone to treat prostate cancer obviate the rejection under 35 USC 103(a).” MYL Ex. 1015 at 2.

A second pair of IDSes, dated May 9, 2014, listed a number of additional references. MYL Exs. 1074-75. These IDSes provided statements of opposition filed in the European Patent Office for a counterpart foreign application of the ’438 patent; Applicants’ response to the opposition; and a number of additional references. *See, e.g.*, MYL Ex. 1075. Additional Information Disclosure Statements filed on May 30, 2014, provided more of the same. MYL Exs. 1076-77. A fourth Notice of Allowance issued on June 2, 2014, reiterating the same grounds for allowance as the previous notice. MYL Ex. 1016.

D. Claim Construction (37 C.F.R. §§ 42.100(b), 42.104(b)(3))

Pursuant to 37 C.F.R. § 42.100(b), a claim in an unexpired patent is given its broadest reasonable interpretation in light of the specification. *Cuozzo Speed Techs., LLC v. Lee*, No. 15-446, 2016 WL 3369425 (U.S. June 20, 2016). Petitioner submits for purposes of this petition only that the terms in the claims of the ’438 patent do not have any special meanings and are presumed to take on their

broadest reasonable meaning consistent with the understanding of a person of ordinary skill in the art (“POSA”) when read in light of the ’438 patent’s specification. Because the claim construction standard in an *inter partes* review is different than that used in litigation, Petitioner reserves the right to present different constructions of terms in litigation under claim construction standards appropriate for those cases. *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

The following terms in the claims of the ’438 patent should be construed for purposes of this petition as they are defined in the specification of the ’438 patent; the Board adopted each of these constructions in the Institution Decision (Paper No. 14) in IPR2016-00286:

- The terms “treat,” “treating” and “treatment” should be construed to mean: “***include*** the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.” MYL Ex. 1001, col. 3, ll. 46–50 (emphasis added).³

³ In its co-pending district court litigation, Petitioner argues that “treat,” “treating,” and “treatment,” properly construed, encompass both palliative and anti-cancer effects, consistent with the Board’s claim construction in the institution decision in IPR2016-00286. *See BTG Int’l Ltd. v. Actavis Labs. FL, Inc.*, No. 15-cv-5909-

- The term “anti-cancer agent” should be construed to mean: “any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells.” MYL Ex. 1001, col. 4, ll. 8–16.
- The term “refractory cancer” should be construed to mean: “cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment.” MYL Ex. 1001, col. 4, ll. 23–27.

See also MYL Ex. 1002, Garnick Decl. ¶¶47-53.

E. Scope and Content of the Prior Art

1. Overview

The '438 patent has a single independent claim that is directed to a method for treating prostate cancer comprising administering therapeutically effective amounts of abiraterone acetate, a CYP17 inhibitor, in combination with prednisone, a glucocorticoid. MYL Ex. 1001, claim 1; MYL Ex. 1002, Garnick Decl. ¶54; MYL Ex. 1017, Hofmann Decl. ¶19. However, the prior art taught use of abiraterone acetate as an effective anti-cancer agent that suppresses testosterone synthesis in prostate cancer patients. MYL Ex. 1002, Garnick Decl. ¶¶36, 37, 46, 55. The prior art also taught that concomitant glucocorticoid replacement therapy

KM-JBC (D.N.J.), ECF No. 207 at 2.

might be necessary when administering abiraterone to treat prostate cancer in a patient, and that this was common practice in the treatment of prostate cancer with ketoconazole, another CYP17 inhibitor. MYL Ex. 1002, Garnick Decl. ¶¶58, 66, 78.

The prior art also taught that abiraterone was a more effective CYP17 inhibitor than ketoconazole. For example, the prior art taught that abiraterone acetate was more effective in decreasing testosterone levels in a mammal than ketoconazole. MYL Ex. 1002, Garnick Decl. ¶¶46, 55, 59. The prior art also taught that the combination of ketoconazole and prednisone was a safe and effective treatment for refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶45, 58.

One of skill in the art would have combined abiraterone acetate and prednisone based on the teachings of O'Donnell and Gerber and/or the '213 patent and Gerber for a safe and effective treatment of prostate cancer with a reasonable expectation of success because the prior art taught the combination of ketoconazole and prednisone as safe and effective to treat patients with hormone refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶58–59.

During prosecution, after numerous rejections for obviousness, the Applicants argued that unexpected results rebutted the *prima facie* case of obviousness made by the Examiner. The Applicants argued that the cited prior art

did not teach or suggest that “abiraterone acetate in combination with prednisone would be a particularly useful combination for cancer treatment.” MYL Ex. 1008 at 2. They further argued that commercial success of Zytiga was evidence of non-obviousness of the claimed combination. MYL Ex. 1008 at 3.

However, Gerber taught that some patients with hormone refractory metastatic prostate cancer could derive significant benefit from treatment with ketoconazole and prednisone. MYL Ex. 1002, Garnick Decl. ¶45. Indeed, the administration of ketoconazole in combination with a glucocorticoid such as prednisone or hydrocortisone was a common practice at the time of the invention. MYL Ex. 1002, Garnick Decl. ¶¶41–42, 44, 78. The Examiner did not consider Gerber during prosecution. Quite possibly, this is because Gerber was submitted after the initial notice of allowance, along with dozens of other references.

Because the Examiner did not consider Gerber, the Examiner did not fully appreciate the obviousness of combining a CYP17 inhibitor (such as abiraterone) with a glucocorticoid (such as prednisone).

Applicants also argued that abiraterone and prednisone unexpectedly prolonged overall survival relative to prednisone alone, and that the prior art taught away from combining abiraterone with prednisone. MYL Ex. 1012 at 6. For example, in traversing repeated obviousness rejections over Tannock (MYL Ex. 1006), the Applicants argued that Tannock taught away from use of abiraterone

with prednisone because it showed that there “was no significant difference in overall survival [between prednisone alone and prednisone plus the cancer agent mitoxantrone],” which would have led one of skill in the art to expect “no difference in survival between one cancer agent alone, and that same cancer agent in combination with prednisone.” MYL Ex. 1012 at 6 (brackets in original).

This was an erroneous and misleading inference to make for at least two reasons: (i) the co-administration of prednisone with abiraterone was not intended to enhance the anti-cancer properties of abiraterone, already known in the art to be a very selective CYP17 inhibitor (and consequently a potent inhibitor of peripheral testosterone production), but rather to reduce side effects associated with administering abiraterone; and (ii) the proper comparison for overcoming obviousness over the prior art should have been whether there was any unexpected synergistic anti-cancer benefit of using abiraterone in combination with prednisone, beyond the anti-cancer effect of administering *abiraterone* alone.

While the Examiner did not find Applicants’ arguments regarding unexpected results persuasive, the Examiner also did not fully appreciate the obviousness of the claimed invention or the reason that the claimed invention does not produce unexpected results. For example, in a Final Rejection dated March 4, 2013 maintaining an obviousness rejection of the pending claims, the Examiner explained that “[s]ince abiraterone acetate provide a new mechanism of action in

treating prostate cancer and prednisone is known to be useful in treating refractory prostate cancer, concomitant employment of both compounds into a single method useful for the very same purpose, treating prostate cancer, would be considered *prima facie* obvious.” MYL Ex. 1011 at 3. However, as explained below, CYP17 inhibitors were known in the art for treating prostate cancer, so that the mechanism of action of abiraterone acetate was not new. Additionally, it was known that co-administering a glucocorticoid such as prednisone with a CYP17 inhibitor was necessary as hormone replacement therapy in order to reduce potential side effects of administering a CYP17 inhibitor, not to enhance an anti-cancer benefit.

Moreover, the Examiner committed error in allowing the claims based on the purported “unexpected commercial success” of Zytiga, the name under which abiraterone acetate is marketed in the United States by the Assignee. In particular, the Examiner’s allowance of the claims based on secondary considerations of commercial success of Zytiga was in error because Applicants failed to show the necessary nexus between the claimed invention (which is directed to a method of treating prostate cancer by administering abiraterone acetate and prednisone) and any commercial success of the drug Zytiga, which consists solely of abiraterone acetate.

2. Background of Prostate Cancer and Its Treatment

Prostate cancer is an androgen-dependent disease. MYL Ex. 1002, Garnick Decl. ¶23. The activation of androgen receptors (“AR”) on prostate cells regulates the transcriptional activation of a wide variety of genes involved in promoting the progression and proliferation of prostate cancer. MYL Ex. 1002, Garnick Decl. ¶24. The two most important androgens responsible for activating the AR are testosterone and its derivative dihydrotestosterone (“DHT”). MYL Ex. 1002, Garnick Decl. ¶24.

Testosterone is synthesized primarily in the testes and the adrenals. MYL Ex. 1002, Garnick Decl. ¶24. The treatment options for treating prostate cancer depend to a great extent on whether the prostate cancer is confined or localized to the prostate or whether it has spread to other organs (*i.e.*, metastasized) from the prostate. MYL Ex. 1002, Garnick Decl. ¶25. The goal of treating primary prostate cancer (*i.e.*, prostate cancer localized to the prostate) is to interfere with the proliferation of prostate cancer cells by interrupting production of testosterone and DHT in the testes, or interfering with their function of binding with receptors on prostate cancer cells. MYL Ex. 1002, Garnick Decl. ¶25. However, a significant number of patients do not respond to localized therapy to suppress testosterone, and consequently develop metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶26–27.

The treatment of metastatic prostate cancer requires systemic therapy. MYL Ex. 1002, Garnick Decl. ¶28. An important goal in treating metastatic prostate cancer patients who have undergone localized androgen ablation is to reduce baseline circulating testosterone levels. MYL Ex. 1002, Garnick Decl. ¶28-29. A substantial amount of extratesticular testosterone is produced in the adrenal glands. MYL Ex. 1002, Garnick Decl. ¶28-29. The first-line treatment for metastatic prostate cancer patients since at least the 1980s has involved systemic suppression of extratesticular testosterone production by the peripheral organs, including the adrenal gland, and is commonly referred to as hormone therapy. MYL Ex. 1002, Garnick Decl. ¶28.

In almost all cases, patients with metastatic prostate cancer develop what is referred to as refractory or castration-resistant prostate cancer (“CRPC”), *i.e.*, prostate cancer that does not respond to a reduction in testosterone levels by surgical or chemical means and resumes growth. MYL Ex. 1002, Garnick Decl. ¶31.

The treatment of metastatic refractory prostate cancer typically also comprises the use of secondary hormone therapy to further reduce testosterone production, usually in combination with anti-androgen therapy. MYL Ex. 1002, Garnick Decl. ¶32.

CYP17 inhibitors were known in the art to be useful in the treatment of androgen-dependent cancers, including prostate cancer, by contributing to suppression of peripheral androgen production. MYL Ex. 1002, Garnick Decl. ¶¶36, 43. Ketoconazole, a non-specific inhibitor of 17 α -hydroxylase, an enzyme critical to steroid synthesis, was commonly used off-label in combination with prednisone as a second-line treatment for metastatic refractory prostate cancer at the time of the invention of the '438 patent. MYL Ex. 1002, Garnick Decl. ¶33.

Like ketoconazole, abiraterone is a CYP17 inhibitor. MYL Ex. 1003, (O'Donnell) at 3-4; MYL Ex. 1002, Garnick Decl. ¶¶36, 55. CYP17 inhibitors were known to inhibit CYP17, an enzyme that is critical to androgen synthesis in both the testes and the adrenal cortex. MYL Ex. 1002, Garnick Decl. ¶37. While the CYP17 enzyme is essential for androgen biosynthesis, it also plays an important role in the production of cortisol, a glucocorticoid that is critical to basic metabolic functions including the formation of glucose, cardiovascular function, and the activation of the anti-stress and inflammatory pathways. MYL Ex. 1002, Garnick Decl. ¶38.

When a CYP17 inhibitor is administered to suppress androgen synthesis, as an undesired side effect cortisol production is compromised (*e.g.*, reduced), which interferes with the negative feedback mechanism that usually maintains cortisol levels within the normal physiological range. MYL Ex. 1002, Garnick Decl. ¶¶39–

40. This results in the pituitary gland producing more adrenocorticotrophic hormone (“ACTH”) to stimulate greater production of glucocorticoids, which are formed from ACTH, in part, by a reaction involving CYP17. MYL Ex. 1002, Garnick Decl. ¶40. However, in the presence of a CYP17 inhibitor, the conversion in the CYP17 pathway from ACTH to cortisol cannot occur. MYL Ex. 1002, Garnick Decl. ¶40.

It was known that CYP17 inhibition of cortisol increased ACTH drive (*i.e.*, increased ACTH production), which resulted in a corresponding increase in mineralocorticoids. MYL Ex. 1002, Garnick Decl. ¶41. An increase in mineralocorticoids beyond normal levels, known as “mineralocorticoid excess,” was known to have adverse effects, including hypertension, hypokalemia (decrease in circulating potassium levels), and fluid retention. MYL Ex. 1002, Garnick Decl. ¶41. It was general knowledge in the art to administer a glucocorticoid, such as prednisone or hydrocortisone, to a patient with ACTH drive, such as a patient administered a CYP17 inhibitor, to reduce ACTH drive, and consequently, reduce mineralocorticoid excess. MYL Ex. 1002, Garnick Decl. ¶42. Therefore, in a patient being treated for prostate cancer with a CYP17 inhibitor such as ketoconazole, a patient would have been concomitantly administered a glucocorticoid such as prednisone for the purpose of reducing the side effects

associated with increased ACTH drive that result from the CYP17 inhibitor, rather than treating prostate cancer itself. MYL Ex. 1002, Garnick Decl. ¶44.

It was known that administration of ketoconazole resulted in adverse side effects including high blood pressure, hypokalemia and swelling associated with ACTH drive and mineralocorticoid excess. MYL Ex. 1002, Garnick Decl. ¶44. Therefore, it was standard practice in the art to co-administer a glucocorticoid when using ketoconazole to treat patients with refractory metastatic prostate cancer. MYL Ex. 1002, Garnick Decl. ¶44.

One of skill in the art would have expected that administering abiraterone, an even more potent inhibitor of CYP17 than ketoconazole, to treat prostate cancer in a patient might also require co-administration of a glucocorticoid, such as prednisone. MYL Ex. 1002, Garnick Decl. ¶¶79-80. One of skill in the art would therefore have appreciated that the co-administration of prednisone with abiraterone was not intended to enhance the clinically-relevant anti-cancer effect of abiraterone. MYL Ex. 1002, Garnick Decl. ¶¶83-84. Instead, one of skill in the art would have expected that the co-administration of prednisone with abiraterone would improve the safety and tolerability of administering abiraterone by reducing the potential for side effects associated with the administration of a CYP17 inhibitor. MYL Ex. 1002, Garnick Decl. ¶44.

3. Prior Art References

a. **In 2004, O'Donnell Described the Administration of Abiraterone Acetate as More Effective for Treating Metastatic Refractory Prostate Cancer than Ketoconazole, and Possibly Requiring Concomitant Glucocorticoid Replacement Therapy**

O'Donnell, A. *et al.*, "Hormonal impact of the 17 α -hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer," *Brit. J. Cancer*, 90:2317–2325 (2004) (MYL Ex. 1003), published on May 18, 2004. O'Donnell is prior art to the '438 patent under at least 35 U.S.C. § 102(b) (pre-AIA) because it was published on May 18, 2004, more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the '438 patent.

O'Donnell taught that abiraterone acetate is a CYP17 inhibitor that suppresses testosterone synthesis in patients with prostate cancer. MYL Ex. 1003, O'Donnell, at Abstract. O'Donnell reported that repeated treatment of male patients with prostate cancer with intact gonadal function (testicular function) with abiraterone acetate at a dose of 500–800 mg can successfully suppress testosterone levels to the castrate range. *Id.* O'Donnell also taught that the dose of abiraterone acetate administered to a particular patient may need to be adjusted in order to attain suppression of testosterone levels at target levels. *See, e.g.*, MYL Ex. 1003, O'Donnell, at Abstract, 2324. O'Donnell also reported that adrenocortical

suppression (*i.e.*, suppression of cortisol) may necessitate concomitant administration of replacement glucocorticoid with abiraterone acetate. *Id.*

O'Donnell reported that as much as 10% of baseline circulating testosterone remains in castrated men due to peripheral conversion of adrenal steroids (DHEA and androstenedione) to testosterone. MYL Ex. 1003 at 2317. O'Donnell explained that this baseline circulating testosterone can activate overexpressed androgen receptors in hormone-refractory tumors. MYL Ex. 1003 at 2317.

O'Donnell also described ketoconazole as an inhibitor of CYP17 that has shown anti-cancer activity for prostate cancer by decreasing the production of adrenal steroids. MYL Ex. 1003 at 2318. O'Donnell also described abiraterone acetate as a more selective CYP17 inhibitor than ketoconazole of the CYP17 enzyme, which will more effectively decrease the production of adrenal steroids. *Id.* O'Donnell further reported that the activity of ketoconazole as a second-line agent in clinical trials among patients with prostate cancer supports the concept of a more selective inhibitor of the CYP17 enzyme. *Id.*

O'Donnell described the potential utility of abiraterone acetate as an effective anti-cancer agent for treating both castrate and non-castrate patients with advanced prostate cancer. O'Donnell reported the results of three separate Phase I studies in which human patients with advanced prostate cancer, including patients who had progressed despite prior hormone and antiandrogen therapy, were treated

with 500–800 mg abiraterone acetate and maintained testosterone suppression at target levels. MYL Ex. 1003 at 2318-19, 2322–23.

In one study, a single-dose study in surgically or medically castrate male patients with advanced prostate cancer, a dose of 500 mg of abiraterone acetate was considered necessary to suppress testosterone to target levels. MYL Ex. 1003 at 2320.

In a second study, a single-dose study involving non-castrate male patients with advanced prostate cancer, there appeared to be a steep dose-response relationship. O'Donnell reported that at a dose of 500 mg of abiraterone acetate, treated patients showed persistent reductions in testosterone levels. MYL Ex. 1003 at 2323.

In a third, multi-dose study involving non-castrate male patients with advanced prostate cancer, O'Donnell reported that a dose of at least 800 mg was required to maintain testosterone suppression at target levels. MYL Ex. 1003 at 2323.

In addition, O'Donnell reported that repeated treatment of non-castrate patients with advanced metastatic prostate cancer with abiraterone acetate at a dose of 800 mg/day can successfully suppress testosterone levels to the castrate range. MYL Ex. 1003 at 2320–2322.

O'Donnell further reported that from the repeat-dose studies, it can be seen that a dose of at least 800 mg is required to maintain testosterone suppression at target levels in these patients. MYL Ex. 1003 at 2323.

O'Donnell also reported that adrenocortical suppression (*i.e.*, the suppression of androgens secreted in the adrenal cortex) may necessitate concomitant administration of replacement glucocorticoid. MYL Ex. 1003 at 2323. In particular, O'Donnell reported that “[a]lthough baseline cortisol levels remained normal, all patients treated at 500 and 800 mg in the multiple dose study developed an abnormal response to a short Synacthen test by Day 11,” indicating a decrease in cortisol level. MYL Ex. 1003 at 2323. O'Donnell further noted that “some impact on cortisol levels was expected from the effect of abiraterone acetate on the steroid synthesis pathway.” MYL Ex. 1003 at 2323. O'Donnell further disclosed that in the clinical use of ketoconazole, “it is common practice to administer supplementary hydrocortisone and this may prove necessary with ... abiraterone acetate.” MYL Ex. 1003 at 2323. On the basis of the clinical evidence, O'Donnell reported that the need for concomitant therapy of abiraterone acetate with a glucocorticoid needed to be investigated further. MYL Ex. 1003 at 2323.

b. In 1990, Gerber Disclosed the Use of Ketoconazole with Prednisone, a Glucocorticoid, in Patients with Hormone Refractory Metastatic Prostate Cancer

Gerber G.S. *et al.*, “Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic prostate cancer,” J. Urol., 144:1177–9 (November 1990) (MYL Ex. 1004), published in November 1990. Gerber is prior art to the ’438 patent under at least 35 U.S.C. § 102(b) (pre-AIA) because it was published more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the ’438 patent. Gerber was submitted in a post-allowance IDS dated October 3, 2013. Gerber was therefore of record, but neither asserted by the Examiner nor argued by the Applicants, during prosecution of the ’438 patent.

Gerber described ketoconazole as “a potent inhibitor of gonadal and adrenocortical steroid synthesis.” MYL Ex. 1004 at 1177. Gerber also described the known cytotoxic effects of ketoconazole on prostate cancer cells and suggested ketoconazole’s potential role in the treatment of prostate cancer. MYL Ex. 1004 at 1177.

Gerber taught the use of ketoconazole, a known CYP17 enzyme inhibitor and a potent inhibitor of gonadal and adrenocortical steroid synthesis, with prednisone in patients with hormone refractory metastatic prostate cancer. MYL Ex. 1004 at Abstract. In particular, Gerber taught that patients having progressive

prostate cancer despite androgen ablation, and therefore unresponsive to initial hormonal therapy, may benefit from the combination of ketoconazole and prednisone. MYL Ex. 1004 at Abstract, 1179.

The Gerber study combined daily administration of 600–900 mg ketoconazole with the administration of 5 mg prednisone twice daily. MYL Ex. 1004 at 1177–78. Gerber showed that 80% (12 out of 15) of patients with prostate cancer characterized by progressively increasing prostate specific antigen (“PSA”) levels experienced a decrease in PSA levels in response to treatment with ketoconazole and prednisone. MYL Ex. 1004 at 1178–79. Gerber also showed that 75% of the patients who had bone pain and/or other symptoms of advancing malignancy at the outset of the study had subjective improvement. MYL Ex. 1004 at 1178–79. Gerber further reported that 20% (3 out of 15) of patients experienced a prolonged (8- to 10-month) favorable response to ketoconazole and prednisone based on persistently decreasing PSA levels and symptomatic improvement, including improvement in bone pain. MYL Ex. 1004 at 1178–79. Gerber further reported that this response rate was similar to that found in studies assessing response by monitoring changes in measurable tumor size, bone scan abnormalities and acid phosphatase. MYL Ex. 1004 at 1179. Gerber concluded that some patients with progressive prostate cancer despite previous hormone therapy will

derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy. MYL Ex. 1004 at 1179.

c. In 1997, the '213 Patent Disclosed Abiraterone Acetate and Its Superiority over Ketoconazole in Treating Prostate Cancer

U.S. Patent 5,604,213 (“the ’213 patent,” MYL Ex. 1005), entitled “17-Substituted Steroids Useful in Cancer Treatment,” issued to Barrie *et al.* on February 18, 1997. The ’213 patent is prior art to the ’438 patent under at least 35 U.S.C. § 102(b) (pre-AIA) because it issued more than one year prior to August 25, 2006, the earliest effective filing date for the claims of the ’438 patent.

The ’213 patent is listed in the FDA’s Orange Book for Zytiga. The ’213 patent is not related to the ’438 Patent and there is no overlap in inventorship between the ’213 patent and the ’438 Patent. The ’213 patent is assigned on its face to British Technology Group, Ltd. Of note, the ’213 patent is incorporated by reference in the ’438 patent, but the ’213 patent was neither argued nor disclosed to the PTO in an IDS during prosecution of the ’438 patent.

The ’213 patent relates to a novel class of 17-substituted steroids and their use in the treatment of androgen-dependent and estrogen-dependent disorders, especially prostatic cancer and breast cancer, respectively. MYL Ex. 1005 at col. 1, ll. 11–14. The compounds disclosed and claimed in the ’213 patent include abiraterone generally, and its acid addition salts and 3-esters (*see, e.g.*, MYL Ex.

1005 at col. 5, ll. 21–26; Example 2 at col. 11, ll. 36–55), as well as abiraterone acetate in particular (*see, e.g.*, MYL Ex. 1005 at col. 10, l. 62 – col. 11, l. 35 (Example 1)).

The '213 patent further disclosed that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition comprising a therapeutically effective amount of the compound, which the '213 patent further disclosed to be 20–800 mg of abiraterone acetate per patient, per day. MYL Ex. 1005 at col. 10, ll. 27–57.

The '213 patent disclosed that the CYP17 enzyme complex is known to be essential for the biosynthesis of androgens and estrogens. MYL Ex. 1005 at col. 1, ll. 17–19. The '213 patent further disclosed that in the treatment of androgen-dependent disorders, especially prostatic cancer, there is a need for strong CYP17 inhibitors. MYL Ex. 1005 at col. 1, ll. 19–22.

The '213 patent reported results from *in vitro* inhibition assays using tissue from the testes of previously untreated human patients undergoing orchiectomy for prostatic cancer. The assays compared the *in vitro* inhibition of 17 α -hydroxyprogesterone, androstenedione, and testosterone production by some of the compounds of the invention, including abiraterone acetate (*i.e.*, Example 1) with that of ketoconazole. MYL Ex. 1005 at col. 21, l. 26–25, l. 12. The '213 patent

reported the IC50 for abiraterone acetate as 0.0097 against lyase and 0.0130 against hydroxylase. MYL Ex. 1005 at col. 22, ll. 58–66. By comparison, the '213 patent reported the IC50 for ketoconazole as 0.026 against lyase (*i.e.*, an order of magnitude higher than abiraterone acetate) and 0.065 against hydroxylase. MYL Ex. 1005 at col. 24, ll. 61–62.

The '213 patent further disclosed the results of *in vivo* assays involving male human wild-type mice that compared the effect on organ weight and production of testosterone and luteinizing hormone of administering abiraterone acetate and ketoconazole, respectively. MYL Ex. 1005 at col. 25, l. 13 – col. 26, l. 63. The mice were tested for the presence of testosterone and luteinizing hormone. Post-mortem analyses of the adrenals, prostate, seminal vesicles, testes and kidneys were also conducted. MYL Ex. 1005 at col. 25, ll. 14–40. The results show that the reductions in weight of all of the prostate, seminal vesicles, testes and kidneys were much greater for the test compounds of the invention than for ketoconazole. MYL Ex. 1005 at col. 25, l. 50–26, l. 26; Table 3.

The '213 patent concluded that abiraterone acetate inhibits androgen, and particularly testosterone, synthesis in mammalian assays. MYL Ex. 1005 at col. 26, ll. 27–63; Table 4. The '213 patent further concluded that administering abiraterone acetate yielded a markedly greater decrease in testosterone levels than did administering ketoconazole. MYL Ex. 1005 at col. 26, ll. 32–38.

F. Explanation of Grounds for Unpatentability

1. The Method of Claim 1 was Obvious over Either O'Donnell in view of Gerber (Ground 1) or the '213 Patent in View of Gerber (Ground 2)

a. O'Donnell and the '213 Patent Disclosed the Use of Abiraterone Acetate to Treat Prostate Cancer

Claim 1 is obvious over O'Donnell in view of Gerber (Ground 1) or the '213 Patent in view of Gerber (Ground 2). MYL Ex. 1002, Garnick Decl. ¶¶54–59. Claim 1 is the only independent claim in the '438 patent. Claim 1 is directed to a method for treating prostate cancer in a human comprising administering therapeutically effective amounts of abiraterone acetate, or a pharmaceutically acceptable salt thereof, and prednisone. Because the prior art disclosed both the use of abiraterone acetate to treat prostate cancer, and co-administering prednisone in treatment of prostate cancer with a CYP17 inhibitor, with sufficient motivation to combine, claim 1 was obvious.

Regarding the use of abiraterone acetate, both O'Donnell and the '213 patent taught that abiraterone acetate is a selective CYP17 inhibitor that is more effective than ketoconazole, a CYP17 inhibitor known in the art, in suppressing testosterone levels in a mammal *in vivo*. MYL Ex. 1003, O'Donnell, at 2318, 2322, 2323, 2325; MYL Ex. 1005, the '213 patent, col. 25, l. 13 – col. 26, l. 63. O'Donnell taught that 500–800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including metastatic

refractory prostate cancer. MYL Ex. 1003, O'Donnell, Abstract. The '213 patent disclosed that abiraterone acetate may be administered in a method of treating androgen- and estrogen-dependent disorders, especially prostate cancer, as a pharmaceutical composition. MYL Ex. 1005, the '213 patent, col. 10, ll. 47–56. The '213 patent further disclosed that a therapeutically effective amount of abiraterone acetate comprises a dose of 20–800 mg per patient, per day. MYL Ex. 1005, the '213 patent, col. 10, ll. 55–56. The '213 patent also taught that an abiraterone acetate salt may be administered to a human patient with prostate cancer to treat prostate cancer in said human patient. MYL Ex. 1005, the '213 patent, col. 10, ll. 22–50.

It would therefore have been obvious in light of the teachings of either O'Donnell or the '213 patent to administer a therapeutically effective amount of abiraterone acetate to a human patient with prostate cancer, to treat the patient's prostate cancer.

b. Gerber Disclosed Co-Administering Prednisone with a CYP17 Inhibitor, like Abiraterone Acetate

O'Donnell taught that concomitant hormone replacement therapy with a glucocorticoid may be needed when using abiraterone acetate to treat a prostate cancer in a human patient. *See, e.g.*, MYL Ex. 1003, O'Donnell, Abstract, 2323. Gerber taught that the combination of ketoconazole and prednisone (a glucocorticoid) is safe and effective in treating human patients with hormone-

refractory advanced prostate cancer. Exhibit 1005, Gerber, Abstract, 1177–1178, 1179. One of skill in the art would have been motivated to add prednisone to a method of using abiraterone acetate (a CYP17 inhibitor) to treat prostate cancer in a human patient by Gerber’s teaching that administering 5 mg prednisone twice daily with ketoconazole, also a CYP17 inhibitor, is a safe and effective treatment in human patients with hormone-refractory prostate cancer. MYL Ex. 1004, Gerber, Abstract 1177–1178, 1179. One of skill in the art could also have been motivated by suggestions in the prior art that prednisone could have some amount of anti-cancer activity. MYL Ex. 1002, Garnick Decl. ¶¶ 33, 89–90.

As such, the skilled artisan would have expected that adding 10 mg of prednisone daily, according to Gerber, to the treatment regimen of O’Donnell, also would be safe and effective in treating a prostate cancer, including prostate cancer refractory to anticancer therapy, including hormone and anti-androgen therapy.

Alternatively, the ’213 patent taught that abiraterone acetate is a CYP17 inhibitor that is more effective than ketoconazole, a CYP17 inhibitor known in the art, in suppressing testosterone levels in a mammal *in vivo*. MYL Ex. 1005, the ’213 patent, col. 25, l. 13 – col. 26, l. 63. Gerber taught that combining ketoconazole with prednisone was safe and effective in treating human patients with hormone-refractory prostate cancer. MYL Ex. 1004, Gerber, Abstract, 1177–1178, 1179. The motivation to add prednisone to the method of treating prostate

cancer of the '213 patent is clearly seen in Gerber who teaches that the administration of ketoconazole, a CYP17 inhibitor, in combination with 5 mg prednisone twice daily, is safe and effective in treating human patients with hormone-refractory prostate cancer. MYL Ex. 1004, Gerber, Abstract 1177– 1178, 1179. As such, the skilled artisan would expect that adding 5 mg twice daily prednisone to the treatment regimen of the '213 patent would also be safe and effective in treating a prostate cancer in such patients, including prostate cancer refractory to anti-cancer therapy, including hormone and anti-androgen therapy.

Therefore, based on the teaching of either O'Donnell in view of Gerber or the '213 patent in view of Gerber, one of skill in the art would have been motivated to co-administer 10 mg of prednisone daily with abiraterone acetate, a more selective CYP17 inhibitor than ketoconazole, to treat a human patient with prostate cancer, including prostate cancer refractory to previous anti-cancer therapy, including hormone and anti-androgen therapy, with a reasonable expectation that such treatment would be successful. One of skill in the art could also have been motivated by suggestions in the prior art that prednisone could have some amount of anti-cancer activity, with a similar expectation. MYL Ex. 1002, Garnick Decl. ¶¶ 33, 89–90.

Claims 2–20 all depend directly or indirectly from claim 1, and include additional limitations combining one or more of the following: i) the amount

and/or dosage range of abiraterone acetate or a pharmaceutically acceptable salt thereof to be administered; ii) the amount and/or dosage range of prednisone to be administered; iii) the type of prostate cancer to be treated; and iv) whether the patient has been previously treated with another anti-cancer agent, where the additional anti-cancer agent may be a hormonal ablation agent, an anti-androgen agent, or an anti-neoplastic agent. MYL Ex. 1002, Garnick Decl. ¶60. For the reasons set forth above regarding claim 1, and additionally for the reasons set forth below, these additional limitations also were obvious over O'Donnell in view of Gerber and/or the '213 patent in view of Gerber. MYL Ex. 1002, Garnick Decl. ¶¶60–76.

2. O'Donnell and the '213 Disclosed the Dosing Limitations Recited in Claims 2 and 3

O'Donnell taught that 500–800 mg of abiraterone acetate can be useful in suppressing testosterone levels in a human patient with prostate cancer, including advanced prostate cancer. *See, e.g.*, MYL Ex. 1003, O'Donnell, Abstract, 2318. The '213 patent taught that a therapeutically effective amount of abiraterone acetate for treating prostate cancer in a human patient includes 20–800 mg/day. MYL Ex. 1005, the '213 patent, col. 10, ll. 47–56.

A therapeutically effective amount of 500–800 mg of abiraterone acetate, as taught by O'Donnell, or 20–800 mg per day of abiraterone acetate, as taught by the '213 patent, is within the claimed ranges of “about 50 mg/day to about 2000

mg/day” (claim 2) and “about 500 mg/day to about 1500 mg/day” (claim 3). *See* MYL Ex. 1001, claims 2 & 3; MYL Ex. 1003, O’Donnell, Abstract; MYL Ex. 1005, the ’213 patent, col. 10, ll. 47-56. Therefore, the daily dosage amounts and ranges of abiraterone acetate recited in these claims were disclosed in both O’Donnell and the ’213 patent. MYL Ex. 1002, Garnick Decl. ¶¶61–62.

Therefore claims 2 and 3 were obvious over O’Donnell in view of Gerber (Ground 1) or the ’213 patent in view of Gerber (Ground 2). MYL Ex. 1002, Garnick Decl. ¶¶61–62.

3. The Dose Recited in Claim 4 was Disclosed to One of Skill in the Art by either O’Donnell or the ’213 Patent

O’Donnell disclosed a dose of 500–800 mg/day of abiraterone acetate used in Phase 1 human studies. MYL Ex. 1003, Abstract, 2319. The ’213 patent disclosed using 20–800 mg/day of abiraterone acetate. MYL Ex. 1005, the ’213 patent, col. 10, ll. 55–56. O’Donnell reported that a dose of 800 mg of abiraterone acetate “can successfully suppress testosterone levels to the castrate range[, but] this level of suppression may not be sustained in all patients due to compensatory hypersecretion of LH” (luteinizing hormone). MYL Ex. 1003, O’Donnell, Abstract. O’Donnell therefore concluded from the studies that in the face of increased LH, higher doses of abiraterone acetate may be required. *See, e.g.*, MYL Ex. 1003, O’Donnell, Abstract; 2324.

It would have been obvious to one of skill in the art to optimize, to 1000 mg/day, the dose of abiraterone acetate administered to treat prostate cancer in a human patient, based on O'Donnell's teaching that adjustments in the dosage amount of abiraterone acetate may be necessary to treat a patient. In addition, with respect to both O'Donnell and the '213 patent, optimizing the dosage range and dosage regimen when administering active ingredients was well within the abilities of an ordinary skilled artisan in the pharmaceutical sciences as of at least 2006.

Thus, based on the teachings of O'Donnell or the '213 patent, it would have been well within the skill of one in the art to optimize the amount of abiraterone acetate to be administered to treat prostate cancer in a human patient, and obvious to do so. MYL Ex. 1002, Garnick Decl. ¶¶61–64.

4. The Dose Recited in Claim 5 was Disclosed to One of Skill in the Art by O'Donnell

O'Donnell teaches that capsules containing 10, 50, 100, and 200 mg of abiraterone acetate were provided for three Phase 1 clinical studies. MYL Ex. 1003, O'Donnell, 2319. It would have required only routine experimentation to increase the amount of abiraterone acetate in the capsules from 200 mg to 250 mg. *Id.*; *see also* MYL Ex. 1002, Garnick Decl. ¶65. Motivation for making this increase includes the starting dose of 500 mg in Study C and the use of 500 mg of abiraterone in Studies A and B, each of which is a multiple of 250 mg. MYL Ex. 1003, O'Donnell, 2319; *see also* MYL Ex. 1002, Garnick Decl. ¶65. Therefore,

one of skill in the art would have made a 250-mg dosage form of abiraterone acetate for the convenience of dosing. MYL Ex. 1002, Garnick Decl. ¶65. For at least this reason, claim 5 is obvious over O'Donnell in view of Gerber.

5. Claims 6–9 were Obvious over O'Donnell or the '213 Patent in View of Gerber

Claims 6–9 are directed to the amount or range of amounts of prednisone administered to a patient: “about 0.01 mg/day to about 500 mg/day” (claim 6); “about 10 mg/day to about 250 mg/day” (claim 7); “about 10 mg/day” (claim 8); and “one dosage form comprising about 5 mg of prednisone” (claim 9). MYL Ex. 1001. Gerber disclosed each of these limitations when it taught that the combination of ketoconazole, a CYP17 inhibitor, and 5 mg of prednisone twice daily is safe and effective in treating patients with hormone-refractory advanced prostate cancer. MYL Ex. 1004, Gerber. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 6 depends from claim 1 and was therefore obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further for the disclosure in Gerber of 10 mg/day of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 7 depends from claim 6 and narrows the claimed range to about 10 mg/day to about 250 mg/day of prednisone. Because Gerber disclosed 10 mg/day of prednisone, claim 7 was obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further

for the disclosure in Gerber of 10 mg/day of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 8 depends from claim 7 and narrows the range to about 10 mg/day of prednisone. Because Gerber disclosed 10 mg/day of prednisone, claim 8 was obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further for the disclosure in Gerber of 10 mg/day of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

Claim 9 depends from claim 1 and requires the dosage form to include about 5 mg of prednisone. Because Gerber disclosed administering 5 mg of prednisone twice daily, a dosage form of 5 mg of prednisone would have been obvious. As such, claim 9 was obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the same reasons that claim 1 was obvious and further for the disclosure in Gerber of administering 5 mg of prednisone. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

6. Claim 10 was Obvious over O'Donnell or the '213 Patent in View of Gerber

Claim 10 depends from claim 1 and recites the limitations of about 500 mg/day to about 1500 mg/day of abiraterone acetate and about 0.01 mg/day to about 500 mg/day of prednisone. MYL Ex. 1001. These limitations are also recited in claims 3 and 6, respectively. Therefore claim 10 was invalid as being obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for

the reasons set out above for claims 1, 3 and 6. MYL Ex. 1002, Garnick Decl. ¶¶66–70.

7. Claim 11 was Obvious over O'Donnell or the '213 Patent in View of Gerber

Claim 11 depends from claim 10 and recites the limitations of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. MYL Ex. 1001. These limitations are also recited in claims 4 and 8, respectively. Claim 11 was therefore invalid as being obvious over O'Donnell in view of Gerber or the '213 patent in view of Gerber for the reasons set out above for claims 1, 4, 8, and 10. MYL Ex. 1002, Garnick Decl. ¶¶61–64.

8. Claims 12–16 were Obvious over O'Donnell in View of Gerber

Claim 12 depends from claim 1 and includes the limitations of the prostate cancer being refractory prostate cancer. Claim 13 depends from claim 12 and requires the refractory prostate cancer to be not responding to at least one anti-cancer agent. Claim 14 depends from claim 13 and required the anti-cancer agent to be a hormonal ablation agent, an anti-androgen agent or an anti-neoplastic agent. Claim 15 depends from claim 14 and requires the hormonal ablation agent to be deslorelin, leuprolide, goserelin, or triptorelin. Claim 16 depends from claim 14 and requires the anti-androgen agent to be bicalutamide, flutamide, or nilutamide.

The patients in the Phase I trial reported in O'Donnell were classified as having advanced or metastatic refractory prostate cancer. MYL Ex. 1003, O'Donnell, Abstract, 2318–2319. In addition, one of the cohorts in O'Donnell had undergone hormone ablation surgery, *i.e.*, orchiectomy, and all three cohorts of patients in O'Donnell had previously undergone hormone or anti-androgen therapy or both, and therefore had been previously treated with at least one anti-cancer agent, and in particular a hormone ablation agent or anti-androgen agent. MYL Ex. 1003, O'Donnell, Abstract; 2318–2320. In Study A, all patients had received flutamide or cyproterone acetate, the former being an anti-androgen agent recited in claim 16, and were receiving goserelin or leuporelin, hormone ablation agents. MYL Ex. 1003, O'Donnell, 2320. Therefore claims 12 and 13 were obvious for the reasons set forth for claim 1 and additionally because O'Donnell taught that abiraterone acetate may be administered to treat a human patient with metastatic prostate cancer that is refractory to at least one anti-cancer agent. MYL Ex. 1002, Garnick Decl. ¶¶71–72.

Claim 14 was obvious for the reasons set forth for claims 1, 12, and 13 and additionally because O'Donnell taught that all three cohorts of patients in O'Donnell previously underwent hormone or anti-androgen therapy, or both. MYL Ex. 1002, Garnick Decl. ¶73.

Claim 15 was obvious for the reasons set forth for claims 1, 12, 13, and 14 and additionally because O'Donnell taught that the patients in Study A previously underwent hormone ablation therapy with goserelin or leuporelin. MYL Ex. 1002, Garnick Decl. ¶73.

Claim 16 was obvious for the reasons set forth for claims 1, 12, 13, and 14 and additionally because O'Donnell taught that the patients in Study A previously underwent anti-androgen therapy with flutamide. MYL Ex. 1002, Garnick Decl. ¶73.

9. The Docetaxel Treatment in Claim 17 was Part of the Background Knowledge of One of Skill in the Art

Claim 17 depends from claim 14 and includes the limitations that the anti-neoplastic agent is docetaxel.

Docetaxel was well known as an anti-cancer compound, and, in particular, an anti-neoplastic agent at the priority date of the '438 Patent. For instance, U.S. Patent No. 5,688,977 (MYL Ex. 1029) which issued on November 18, 1997, disclosed that docetaxel is an anti-cancer compound. *See id.* at col. 2, ll. 29–32. And docetaxel in combination with prednisone was known to increase overall survival of patients with metastatic refractory prostate cancer, (MYL Ex. 1022, Tannock, Abstract), the first treatment known to do so, and was approved for the treatment of metastatic refractory prostate in 2004. *See*, MYL Ex. 1030, FDA News Release dated May 19, 2004. Therefore, claim 17 was obvious over

O'Donnell in view of Gerber for the reasons set forth for claim 14 and additionally because the background knowledge in the art taught that docetaxel with prednisone was a first-line treatment for metastatic hormone-refractory prostate cancer, known to increase overall survival. MYL Ex. 1002, Garnick Decl. ¶74.

10. Claim 18 was Obvious over O'Donnell in View of Gerber

Claim 18 depends from claim 12 and includes the limitations from claim 10 of about 500 mg/day to about 1500 mg/day of abiraterone acetate and about 0.01 mg/day to about 500 mg/day of prednisone. MYL Ex. 1001. Claim 18 was therefore invalid as obvious over O'Donnell in view of Gerber for the reasons set out above for claims 10 and 12. MYL Ex. 1002, Garnick Decl. ¶¶66–70, 75.

11. Claim 19 was Obvious over O'Donnell in View of Gerber

Claim 19 depends from claim 18 and includes the limitations from claim 11 of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. MYL Ex. 1001. Claim 19 was therefore invalid as obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 18. MYL Ex. 1002, Garnick Decl. ¶76.

12. Claim 20 was Obvious over O'Donnell in View of Gerber

Claim 20 depends from claim 17 and includes the limitations from claim 11 of about 1000 mg/day of abiraterone acetate and about 10 mg/day of prednisone. Claim 20 was therefore invalid as obvious over O'Donnell in view of Gerber for the reasons set out above for claims 11 and 17. MYL Ex. 1002, Garnick Decl. ¶76.

G. Secondary Considerations do not Indicate that the Claims of the '438 Patent were Non-Obvious

To counter the *prima facie* evidence that all claims of the '438 patent are obvious, the patent owner may try to rely on secondary considerations of non-obviousness. While any such evidence would be “insufficient” to “overcome the strong showing of obviousness” here, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007), petitioner nonetheless preliminarily addresses certain alleged secondary considerations below, and reserves the right to respond to any arguments by the patent owner asserted in this proceeding.

1. Applicants did not Offer Relevant Evidence of Commercial Success and the Examiner Issued the '438 Patent Based on the Erroneous Conclusion that the Asserted Commercial Success of Zytiga Overcame the Obviousness of the Claimed Invention.

Applicants asserted during prosecution that the commercial success of Zytiga, a commercial product containing abiraterone acetate, was evidence of the non-obviousness of the claimed invention. MYL Ex. 1012 at 8. The Examiner erroneously concluded that the alleged “unexpected commercial success of the launch of the drug”, Zytiga, obviated the obviousness rejection over O'Donnell and Tannock. MYL Ex. 1013; MYL Ex. 1014; MYL Ex. 1015; MYL Ex. 1017, Hofmann Decl. ¶20. This was error.

It is well settled that evidence of secondary considerations, such as commercial success, is only relevant to an obviousness analysis if the patentee can

show a direct link, or nexus, between the alleged secondary consideration and the claims of the patent. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). In addition, the proffered evidence must be commensurate in scope with the asserted claims. *Id.* Commercial success must be derived from the claimed invention. *Smith & Nephew, Inc. v. ConvaTec Techs., Inc.*, Case Nos. IPR2013-00097 and IPR2013-00102 (PTAB May 29, 2014); MPEP § 716.03(b).

An applicant asserting commercial success to overcome an obviousness rejection bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success. MPEP § 716.03.

During prosecution, Applicants alleged that Zytiga's market shares of 70% in the "post-chemo" mCRPC market prior to the launch of Xtandi and 57% after the launch of Xtandi indicated that the claimed invention was a commercial success. MYL Ex. 1012 at 7-8, slide 12. But this information was misleading and incomplete, and could not suffice as a basis for allowing the '438 patent because Zytiga was not an unexpected commercial success when viewed in the proper market context. MYL Ex. 1017, Hofmann Decl. ¶¶ 35–38. Further, even assuming that the market definition Applicants used is accurate (and it is not), or that Applicants put Zytiga in the proper market context (which they did not), this information is insufficient as a matter of law because it fails to show any nexus

between the claimed combination and the commercial performance of Zytiga. MYL Ex. 1017, Hofmann Decl. ¶¶29–34.

Even assuming that Zytiga's commercial performance has been strong, regardless of how broadly the relevant therapeutic market is defined, any commercial success of Zytiga® has not been shown to derive from the claimed invention, *i.e.*, the combination of abiraterone acetate and prednisone. MYL Ex. 1017, Hofmann Decl. ¶¶29–35. Certainly, Applicants made no effort during prosecution of the '438 patent to show any nexus between the claimed invention and the commercial success of Zytiga®. Instead, any commercial success of Zytiga® is likely due to the effectiveness of abiraterone acetate, in isolation, in treating prostate cancer.

In particular, Applicants presented no evidence to suggest that the claimed invention, rather than the prior art abiraterone acetate, was responsible for any commercial success of Zytiga.® Instead, Applicants misled the Examiner by arguing that because Zytiga® is approved in combination with prednisone, Zytiga® is a commercial embodiment of the claimed invention. MYL Ex. 1012 at 7. Applicants then extrapolated that the sales of Zytiga® were evidence of the commercial success of the invention. However, this is incorrect as a matter of law because Zytiga® is the trade name under which abiraterone acetate is marketed.

And abiraterone acetate by itself is not a commercial embodiment of the claimed invention. Specifically, the active ingredient in Zytiga® is abiraterone acetate.

Abiraterone acetate and its use in treating prostate cancer are claimed in the '213 patent. Therefore, Zytiga® is a commercial embodiment of the '213 patent, not the '438 patent. In order to overcome the Examiner's *prima facie* case of obviousness by arguing commercial success, Applicants were required to provide sufficient evidence of a nexus between the commercial performance of Zytiga® and any incremental clinically significant anti-cancer benefit of administering the combination of abiraterone acetate and prednisone over abiraterone alone.

Applicants provided no such evidence. Having failed to do so, Applicants failed to meet their burden of proof.

2. One of Skill in the Art would not Anticipate Unexpected Benefits from the Claimed Invention and Applicants did not Offer Any Evidence of Relevant Unexpected Results

Although Zytiga® is approved in combination with prednisone, as Dr. Garnick explains, the anti-cancer effect of administering Zytiga® to treat prostate cancer is obtained from abiraterone acetate. MYL Ex. 1002, Garnick Decl. ¶93. This is because the prednisone administered with abiraterone in accordance with the approved indication for Zytiga® is intended as hormone replacement therapy related to administration of a CYP17 inhibitor, and not as an anti-cancer therapy. MYL Ex. 1002, Garnick Decl. ¶¶78–80, 84–88. Therefore, one of skill would not

expect the administration of the combination of abiraterone acetate and prednisone to provide any additional clinically significant anti-cancer benefit in treating prostate cancer beyond the anti-cancer benefit obtained from the administration of abiraterone acetate alone. MYL Ex. 1002, Garnick Decl. ¶¶84, 90.

Importantly, abiraterone acetate was known as an anti-cancer agent at least as of the earliest priority date of the claimed invention. In particular, abiraterone acetate was known as an anti-cancer agent for the treatment of prostate cancer. MYL Ex. 1002, Garnick Decl. ¶¶46, 55. For example, abiraterone acetate for the treatment of prostate cancer was disclosed and claimed in the '213 patent. MYL Ex. 1002, Garnick Decl. ¶¶46, 55, 83. Abiraterone acetate had been shown to reduce testosterone levels in refractory metastatic prostate cancer patients in clinical trials. MYL Ex. 1002, Garnick Decl. ¶¶46, 55. Therefore, the proper comparison for overcoming obviousness over the prior art based on unexpected results should have been whether there was any unexpected synergistic anti-cancer benefit of using the combination of abiraterone and prednisone beyond the anti-cancer effect of abiraterone alone. MYL Ex. 1002, Garnick Decl. ¶¶ 81-83. However, there are no unexpected anti-cancer synergies arising from the co-administering abiraterone acetate and prednisone. MYL Ex. 1002 (Garnick Decl.) ¶¶ 91-93.

But Applicants never once argued unexpected results of administering abiraterone and prednisone over abiraterone alone. Instead, Applicants misled the Examiner by arguing alleged unexpected benefits of abiraterone and prednisone over prednisone and a placebo. *See, e.g.*, July 3, 2012 Response (MYL Ex. 1008), January 11, 2013 Response (MYL Ex. 1010); June 4, 2013 Response (MYL Ex. 1012). However, evidence of any purported benefits of abiraterone and prednisone over prednisone and a placebo is insufficient as a matter of law to overcome a *prima facie* case of obviousness over the closest prior art, *i.e.*, abiraterone disclosed in the '213 patent.

Tellingly, the assignee of the '438 patent and NDA holder, Janssen Biotech Inc., has never described the co-administration of prednisone with Zytiga® as enhancing the anti-cancer activity of Zytiga® in information provided to healthcare practitioners. MYL Ex. 1002, Garnick Decl. ¶¶85–88. Instead, in the prescribing information for Zytiga®, including the 2011 Approval Prescribing Information and the 2015 revised Prescribing Information and accompanying brochure on co-administration, it is explained that co-administration of prednisone with Zytiga® is intended to reduce adverse effects, such as hypertension, hypokalemia and fluid retention that may result from CYP17 inhibition of cortisol production and consequent ACTH drive. MYL Ex. 1018, 2011 Zytiga® Approval Prescribing

Information, at 3–6, 11; MYL Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at 2–3.

For example, the 2015 brochure “Putting Prednisone in Perspective,” that accompanies the 2015 revised Prescribing Information for Zytiga®, states that “[p]rednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with Zytiga®” and that “[c]oadministration of prednisone [with Zytiga®] suppresses the ACTH drive and reduces the incidence and severity of mineralocorticoid excess adverse reactions.” MYL Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at 2.

Indeed, the Zytiga® 2015 Prescribing Information makes clear that prednisone is co-administered as hormone replacement therapy and that “7.5 mg/day to 10 mg/day of prednisone is approximately the physiologic equivalent of the amount of endogenous cortisol normally produced on a daily basis.” MYL Ex. 1019, 2015 Zytiga® Prescribing Information, Co-administration Brochure, at 3.

As Dr. Garnick explains in his accompanying declaration, it was known in the art that administering ketoconazole, a CYP17 inhibitor like abiraterone acetate, to treat a prostate cancer may result in significant side effects, such as hypertension, hypokalemia and fluid retention as a result of a decrease in cortisol levels and consequent ACTH drive. MYL Ex. 1002, Garnick Decl. ¶¶44, 78–80. These adverse effects reduced the safety of administering ketoconazole as a single

agent. MYL Ex. 1002, Garnick Decl. ¶¶44, 78–80. Therefore, it was common practice in the art to co-administer a glucocorticoid as replacement therapy when administering ketoconazole to treat prostate cancer in a human patient in order to improve the safety and enhance the tolerability of treatment. MYL Ex. 1002, Garnick Decl. ¶¶45, 78–80. The particular combination of ketoconazole and prednisone was known to be safe and effective in treating patients with metastatic refractory prostate cancer based on at least the teachings of Gerber. *See, e.g.*, Exhibit 1004, Gerber, Abstract; MYL Ex. 1002, Garnick Decl. ¶¶58–59, 78–80.

Based on at least these teachings, one of skill in the art would have had a reasonable expectation that administration of abiraterone, a CYP17 inhibitor like ketoconazole, to treat a patient with prostate cancer would require the co-administration of a glucocorticoid such as prednisone in order to improve safety and enhance tolerability of administration. MYL Ex. 1002, Garnick Decl. ¶¶58–59, 78–80.

To the extent that the co-administration of prednisone with abiraterone made treatment of prostate cancer with abiraterone safer and/or more tolerable, this greater safety and/or tolerability was expected, based on the teachings of the prior art, including Gerber and others. *See, e.g.*, MYL Ex. 1004, Gerber, Abstract, 1178–1179; MYL Ex. 1020, Harris, 544; MYL Ex. 1021, Oh, Abstract, 89-90;

MYL Ex. 1022, Tannock 2004, 1502; MYL Ex. 1003, O'Donnell, 2323; MYL Ex. 1002, Garnick Decl. ¶¶78–80, 84, 89–90.

3. The '438 Patent Satisfied No Long-Felt but Unmet Need

Patentees may argue that commercial performance of Zytiga® is evidence of long-felt but unmet need. However, as explained by Dr. Hofmann, any success of Zytiga® that is not a result of the alleged novel features of the claimed invention is irrelevant to secondary considerations. MYL Ex. 1017, Hofmann Decl. ¶¶23, 29–34. As Dr. Garnick explains, the combination of abiraterone acetate and prednisone does not produce unexpected results in anti-cancer benefit. MYL Ex. 1002, Garnick Decl. ¶¶84, 90, 93. In fact, the perception among clinicians is that the requirement to co-administer prednisone with Zytiga is a drawback to its use to treat prostate cancer, a drawback not shared by other, competitive, therapies. MYL Ex. 1002, Garnick Decl. ¶¶94–96. For at least these reasons, the combination of abiraterone and prednisone satisfied no long-felt need beyond what abiraterone may have done.

4. The '213 is a Blocking Patent that Limits the Applicability of Commercial Success

The Federal Circuit has held that the existence of a blocking patent limits the applicability of any evidence of commercial success to overcome a prima facie case of obviousness. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376–77 (Fed. Cir. 2005) (where “market entry by others was precluded” as a

result of a patent covering the active ingredient and its method of use and FDA exclusivity, “the inference of non-obviousness of weekly-dosing, from evidence of commercial success, is weak.”). Both abiraterone acetate and its use for the treatment of prostate cancer are claimed in the ’213 patent. MYL Ex. 1002, Garnick Decl. ¶¶46, 55, 83. The FDA’s Orange Book lists the ’213 patent as covering Zytiga®.⁴ Because the ’213 patent claims abiraterone acetate and its use in a method of treating an androgen-dependent disorder, “no entity other than” the patentee “could have successfully brought [abiraterone acetate] to market.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740–41 (Fed. Cir. 2013). The ability of the patentees of the ’213 to block additional research and development of abiraterone acetate limits the relevance of commercial success for the ’438 patent. MYL Ex. 1017, Hofmann Decl. ¶¶22, 24–28.

As Dr. Hofmann explains, from an economic perspective, commercial success presumes that if an idea were obvious to market participants, then others would have brought that idea to market sooner had there been economic incentives to do so. MYL Ex. 1017, Hofmann Decl. ¶27. A finding of commercial success can, in some circumstances, support the notion that a patent was not obvious to

⁴ MYL Ex. 1047, FDA Website, Orange Book, Zytiga (NDA 202379),

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed 6/30/2016)

those skilled in the art if those incentives for development existed. MYL Ex. 1017, Hofmann Decl. ¶21. However, in this case, the '213 patent was a blocking patent that limited economic incentives to develop the invention of the '438 patent. MYL Ex. 1017, Hofmann Decl. ¶¶25–26. As Dr. Hofmann explains, “the existence of the '213 Patent prevents the performance of Zytiga from providing objective evidence of nonobviousness of the '438 Patent.” MYL Ex. 1017, Hofmann Decl. ¶28.

5. Copying by Generic Drug Makers is Irrelevant

Finally, the Patentees may argue that petitioner and other generic drug companies seek to copy the invention of the '438 Patent by commercializing generic versions of abiraterone acetate. Because copying “is required for FDA approval” of generic drugs, any “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

H. Conclusion

For the reasons discussed above, petitioner requests that the Board institute an *inter partes* review and determine that all claims (1–20) of the '438 patent be canceled as unpatentable.

Respectfully submitted,

Dated: June 30, 2016

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

This Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1) because this Petition contains 13,342 words, as determined by the word-count function of Microsoft Word, excluding the parts of the Petition exempted by Rule (i.e., a table of contents, a table of authorities, mandatory notices under 37 C.F.R. § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing).

Date: June 30, 2016

/s/ Brandon M. White
Brandon M. White

*Counsel for Petitioner Mylan
Pharmaceuticals Inc.*

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438 by Federal Express Next Business Day Delivery on this day on the Patent Owner's correspondence address of record for the subject patent as follows:

Janssen Oncology, Inc.
10990 Wilshire Blvd., Suite 1200
Los Angeles, CA 90024

Johnson & Johnson,
Attn: Joseph F. Shirtz
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

and by email to the service addresses for Patent Owner listed in Paper No. 13 in IPR2016-00286:

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Date: June 30, 2016

/s/ Brandon M. White
Brandon M. White

Counsel for Petitioner Mylan Pharmaceuticals Inc.

EXHIBIT F

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WOCKHARDT BIO AG
Petitioner

v.

JANSSEN ONCOLOGY, INC.,
Patent Owner

Case IPR: Unassigned

U.S. Patent No. 8,822,438

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,822,438
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-.80, 42.100-.123**

Mail Stop “PATENT BOARD”
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313–1450

*Petition for Inter Partes Review of U.S. Patent No. 8,822,438***LIST OF EXHIBITS**

<i>Wockhardt Exhibit #</i>	<i>Description</i>
1001	Auerbauch, A. H. & Belldesgrum, A. S., U.S. Patent No. 8,822,438 (filed Feb. 24, 2011; issued Sep. 2, 2014) (“the ’438 patent”)
1002	Declaration of Paul A. Godley, MD, Ph.D., MPP
1003	Dr. Paul A. Godley’s <i>Curriculum Vitae</i>
1004	Gerber, G. S. & Chodak, G. W., “Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic prostate cancer,” <i>J. of Urology</i> , 144(5): 1177-9 (1990) (“Gerber”)
1005	O’Donnell, A. <i>et al.</i> , “Hormonal impact of the 17 α -hydroxylase/C _{17,20} -lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer,” <i>British J. of Cancer</i> , 90: 2317-2325 (2004) (“O’Donnell”)
1006	Sartor, O. <i>et al.</i> , “Effect of prednisone on prostate-specific antigen in patients with hormone-refractory prostate cancer,” <i>Urology</i> , 52: 252-6 (1998) (“Sartor”)
1007	Tannock, I. F. <i>et al.</i> , “Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer,” <i>New Engl. J. Med.</i> , 351: 1502-1512 (2004)
1008	Attard, G. <i>et al.</i> , “Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer,” <i>BJU Inter.</i> , 96:1241-1246 (2005)
1009	Kasper, D. L. <i>et al.</i> (Eds.). (2005). <i>Harrison’s Principles of Internal Medicine</i> , Vol. 1, 16 th ed. New York City, NY: The McGraw-Hill Companies, Inc.
1010	Tannock, I.F. <i>et al.</i> , “Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points,” <i>J. Clin. Oncol.</i> , 14: 1756-1764 (1996).

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Wockhardt Exhibit #	Description
1011	Harris, K.A. <i>et al.</i> , “Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer,” <i>J. of Urology</i> , 168: 542-545 (2002)
1012	Hellerstedt, B. A. and Pienta, K. J., “The current state of hormonal therapy for prostate cancer,” <i>CA Cancer J. Clin.</i> , 52:154-179 (2002)
1013	Trump, D. L. <i>et al.</i> , “High-dose ketoconazole in advanced hormone-refractory prostate cancer: endocrinologic and clinical effects,” <i>J. Clin. Oncol.</i> , 7:1093-1098 (1989)
1014	Costa-Santos, M. <i>et al.</i> , “Two prevalent CYP17 mutations and geno-type-phenotype correlations in 24 Brazilian patients with 17-hydroxylase deficiency,” <i>J. of Clin. Endocrin. & Metab.</i> , 89(1): 49-60 (2004)
1015	Oh, W.K., “Secondary hormonal therapies in the treatment of prostate cancer,” <i>Urology</i> , 60 (Suppl 3A): 87-93 (2002)
1016	Scholz, M. <i>et al.</i> , “Long-term outcome for men with androgen independent prostate cancer treated with ketoconazole and hydrocortisone,” <i>J. of Urology</i> , 173: 1947-1952 (2005)
1017	Fosså, S. D., <i>et al.</i> , “Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European Organization for Research and Treatment of Cancer Genitourinary Group,” <i>J. of Clin. Oncol.</i> , 19(1): 62-71 (2001)
1018	Brassel, S. A. <i>et al.</i> , “Prostate-specific antigen versus prostate-specific antigen density as predictor of tumor volume, margin status, pathologic stage, and biochemical recurrence of prostate cancer,” <i>Urology</i> , 66:1229-1233 (2005)
1019	Berry, W. <i>et al.</i> , “Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer,” <i>J. of Urology</i> , 168: 2439-2443 (2002)

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Wockhardt Exhibit #	Description
1020	U.S. Food and Drug Administration (“FDA”) News Release dated May 19, 2004, “FDA Approves New Indication for Taxotere—Prostate Cancer,” http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108301.htm (last accessed 8/8/2016)
1021	Ryan, C. J. <i>et al.</i> , “Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response,” <i>Clin. Cancer Res.</i> , 17:4854-4861 (2011) (“Ryan 2011”)
1022	Attard, F. <i>et al.</i> , “Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer,” <i>J. of Clin. Oncol.</i> , 27:3742-3748 (2009) (“Attard 2009”)
1023	Ryan, C. J. <i>et al.</i> , “Abiraterone in metastatic prostate cancer without previous chemotherapy,” <i>N Engl J Med</i> , 368:138-148 (2013) (“Ryan 2013”)
1024	Danila, D. C. <i>et al.</i> , “Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer,” <i>J. of Clin. Oncol.</i> , 28:1496-1501 (2010) (“Danila”)
1025	Kelly, W. K. <i>et al.</i> , “Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer,” <i>J. of Clin. Oncol.</i> , 11:607-615 (1993)
1026	Small, E. J. <i>et al.</i> , “Serum prostate-specific antigen decline as a marker of clinical outcome in hormone-refractory prostate cancer patients: association with progression-free survival, pain end points, and survival,” <i>J. of Clin. Oncol.</i> , 19:1304-1311 (2001)
1027	Miller, G. M. & Hinman, Jr., F., “Cortisone treatment in advanced carcinoma of the prostate,” <i>J. of Urology</i> , 72(3): 485-496 (1954)

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Wockhardt Exhibit #	Description
1028	Tannock, I. <i>et al.</i> , “Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response,” <i>J. of Clin. Oncol.</i> , 7(5): 590-597 (1989)
1029	Scher, H. I. & Sawyers, C. L., “Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis,” <i>J Clin Oncol</i> , 23:8253-8261 (2005)
1030	Barrie, S. E. <i>et al</i> , U.S. Patent No. 5,604,213 (filed Sep. 30, 1994; issued Feb. 18, 1997)
1031	File History for U.S. Patent No. 8,822,438
1032	Gilman, A. <i>et al.</i> (Eds.). (1990). <i>The Pharmacological Basis of Therapeutics</i> , 8 th ed. Elmsford, NY: Pergamon Press, Inc., 62-83, 1431-1462
1033	Ganong, W. F. (1979). <i>Review of Medical Physiology</i> . Los Altos, CA: Lange Medical Publications, 277-300
1034	Taxotere Prescribing Information (2004), http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/020449s028lbl.pdf (last accessed 8/8/2016)
1035	Potter, G. A. <i>et al</i> , “Novel steroidal inhibitors of human cytochrome P45017 α (17 α -hydroxylase-C17,20-lyase): potential agents for the treatment of prostate cancer,” <i>J. Med. Chem.</i> , 38:2463-2471 (1995) (“Potter”)
1036	Fakih, M. <i>et al.</i> , “Glucocorticoids and Treatment of Prostate Cancer: A Preclinical and Clinical Reivew,” <i>Urology</i> , 60:553-561 (2002) (“Fakih”)
1037	MacAdams, M. R. <i>et al</i> , “Reduction of serum testosterone levels during chronic glucocorticoid therapy,” <i>Ann Int Med</i> , 104:648-651 (1986)

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Wockhardt Exhibit #	Description
1038	Rajfer, J. <i>et al</i> , “Mechanism of inhibition of human testicular steroidogenesis by oral ketoconazole,” <i>J Clin Endocrinol Metab</i> , 63:1193-1198 (1986)
1039	Santen, R. J. <i>et al</i> , “Site of action of low dose ketoconazole on androgen biosynthesis in men,” <i>J Clin Endocrinol Metab</i> , 57:732 (1983)
1040	Sonino, N., “The use of ketoconazole as an inhibitor of steroid production,” <i>N Engl J of Med</i> , 317:812-817 (1987)
1041	Osol, A. (Ed.). (1980). <i>Remington’s Pharmaceutical Sciences</i> , 16 th ed. Easton, PA: Mack Publishing Company, Ch. 89: 1553-1584 and Ch. 99: 1703-1714
1042	Sartor, O., “Abiraterone prolongs survival in metastatic prostate cancer,” <i>Nat Rev Clin Oncol</i> , 8:515-516 (2011)
1043	Fisher, R. I. <i>et al</i> , “Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin’s lymphoma,” <i>N Engl J Med</i> , 328:1002-1006 (1993)
1044	Bearden, J. D. <i>et al</i> , “Combination chemotherapy using cyclophosphamide, vincristine, methotrexate, 5-fluoruracil, and prednisone in solid tumors,” <i>Cancer</i> , 39:21-26 (1977)
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1046	Scher, H. I. <i>et al</i> , “Targeting the androgen receptor: improving outcomes for castration resistant prostate cancer,” <i>Endocrine-Related Cancer</i> , 11:459-476 (2004)
1047	Yamamoto, M. <i>et al</i> , “Role of prostate-specific antigen and digital rectal examination in the detection of prostate cancer,” <i>Int J Urol</i> , 1:74-77 (1994)

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<i>Wockhardt Exhibit #</i>	<i>Description</i>
1048	Mayo Clinic Website, Prostate cancer, http://www.mayoclinic.org/diseasesconditions/prostate-cancer/basics/definition/con-20029597?p=1 (accessed Aug. 8, 2016)
1049	Cancer.org (ACS), “What are the key statistics about prostate cancer?” http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics (accessed Aug. 8, 2016)
1050	Cancer.net (ASCO Patient Website), Treatment of Metastatic Castration-Resistant Prostate Cancer, http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer (accessed Aug. 9, 2016)
1051	Kirby, M., C. Hirst, and E.D. Crawford (2011), “Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review,” <i>International Journal of Clinical Practice</i> 65(11): 1180-1192
1052	Zytiga Label (Mar. 20, 2015), http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202379s018lbl.pdf (accessed Aug. 9, 2016)
1053	Zytiga Website, How Zytiga [®] (abiraterone acetate) Works, https://www.zytiga.com/print/about-zytiga/how-zytiga-works (accessed Aug. 8, 2016)
1054	Mayo Clinic Website, Hormone Therapy for Prostate Cancer, http://www.mayoclinic.org/tests-procedures/hormone-therapy-for-prostate-cancer/home/ovc-20201738 (accessed Aug. 8, 2016).
1055	FDA Website, Drugs@FDA – Zytiga, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fusection=Search.DrugDetails (accessed Aug. 8, 2016)
1056	FDA News Release, “FDA expands Zytiga’s use for late-stage prostate cancer,” 12/10/2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm (accessed Aug. 8, 2016)

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Wockhardt Exhibit #	Description
1057	Wells Fargo Securities, LLC., “Johnson & Johnson,” 6/29/2015.
1058	FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed Aug. 8, 2016)
1059	Murphy, William J., John L. Orcutt, and Paul C. Remus (2012), <i>Patent Valuation: Improving Decision Making through Analysis</i> , Hoboken, NJ: Wiley
1060	Cowen & Company, “Quick Take – Johnson & Johnson,”
1061	William Blair, “Biotechnology – Zytiga Fourth-Quarter Sales Imply Xtandi Strength,” 1/22/2013
1062	Zytiga Brochure, Putting Prednisone in Perspective, 3/2015
1063	Jevtana Website, Dosing and Administration, http://www.jevtana.com/hcp/dosing/default.aspx (accessed Aug. 8, 2016)
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1077	Declaration of Robert D. Stoner, Ph.D.
1078	Dr. Robert D. Stoner’s <i>Curriculum Vitae</i>
1079	Attard, G. <i>et al.</i> , “Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven,” <i>J Clin Oncol</i> , 26(28):4563-4571 (2008)
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I. Introduction

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Wockhardt Bio AG submits this Petition for *Inter Partes* Review (“IPR”) seeking cancellation of claims 1-20 of U.S. Patent No. 8,822,438 (WCK1001) as unpatentable under 35 U.S.C. § 103(a).

The challenged claims are generally directed to methods of treating prostate cancer comprising administering a therapeutically effective amount of abiraterone acetate and a therapeutically effective amount of prednisone. (WCK1001, 16:16-20.) Dependent claims recite dosage amounts for the abiraterone and prednisone, as well as the type of prostate cancer to be treated. (*Id.*, 16:21-17:14.)

However, every element of the challenged claims existed in the prior art. For instance, abiraterone acetate was a well-known, potent, specific inhibitor of CYP17, an enzyme that functions to produce testosterone: a fuel for prostate cancer growth. And O’Donnell (WCK1005) demonstrates that abiraterone acetate was used to treat prostate cancer by August 25, 2006.¹

Further, using glucocorticoids, such as prednisone, in treating prostate cancer had been known since at least the 1950’s. In fact, Sartor (WCK1006)

¹ Petitioner does not concede that the ’438 patent is entitled to an effective filing date of August 25, 2006, rather that it is not entitled to any earlier date.

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teaches the anti-prostate cancer effect of prednisone. For example, Sartor reports that administering prednisone caused a significant reduction in PSA levels, a primary indicator of prostate cancer tumor burden, in patients participating in clinical trials. In addition, co-administering prednisone with other anti-cancer agents had long been part of the standard of care when treating prostate cancer. (WCK1007, 1509; WCK1029, 8253; WCK1002, ¶¶29, 41-45.) And finally, co-administering prednisone with CYP17 inhibitors, such as ketoconazole, was seen as necessary to prevent unwanted side effects that can result from CYP17 inhibition. (WCK1005, 2323; WCK1011; 542-544; WCK1016, 1947; WCK1040, 814; WCK1002, ¶¶40, 44.)

This petition and the supporting Declaration of Dr. Paul A. Godley (WCK1002), an expert in the diagnosis and treatment of genitourinary cancers, evidence that the challenged claims merely combine the known elements of using abiraterone and prednisone individually to treat prostate cancer, achieving predictable results. As such, each of the challenged claims fall squarely within the Supreme Court's *KSR* decision and its extensive progeny as fatally obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Further, no publicly available evidence of objective indicia of nonobviousness weighs in favor of patentability. Accordingly, this Petition demonstrates that Wockhardt is reasonably likely to prevail with respect to at least one challenged claim.

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II. Grounds for standing (37 C.F.R. § 42.104(a))

Wockhardt certifies that the '438 patent is available for IPR and Wockhardt is not barred or estopped from requesting IPR of any of the challenged claims.

III. Statement of the precise relief requested and the reasons therefore

The Office should institute IPR under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80 and 42.100-42.123, and cancel claims 1-20 of the '438 patent as unpatentable under pre-AIA 35 U.S.C. § 103(a) for the reasons explained below. This petition is accompanied and supported by the declarations of Dr. Paul A. Godley (WCK1002), an expert in the diagnosis and treatment of genitourinary cancers, and Dr. Robert Stoner (WCK1077), an expert in industrial organization and economics. Wockhardt's detailed, full statement of the reasons for relief requested is provided in § VI.

IV. Overview

A. Person of ordinary skill in the art ("POSA")

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '438 patent, a POSA would be a treating clinician specializing in oncology, typically holding an M.D. degree, with at least five years of experience specializing in medical oncology. (WCK1002, ¶17.) Alternatively, a POSA would have an M.D., with at least five years of experience specializing in urology and at least two years of clinical experience. (*Id.*) A POSA

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would have also typically worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others in the team, to solve a given problem. (*Id.*) For example, such a team may be comprised of a biochemist (who, *e.g.*, would have knowledge relating to enzyme inhibition), an endocrinologist (who, *e.g.*, would have knowledge relating to hormone-directed treatments), and a pharmaceutical scientist (who, *e.g.*, who have knowledge related to developing pharmaceutical dosage forms). (*Id.*)

Before August 25, 2006, a POSA would have been aware of the teachings provided by the references discussed in this Petition and by Dr. Godley, who also discusses prior art teachings confirming the general knowledge of a POSA.

See Abbott Labs. v. Andrx Pharm., Inc., 452 F.3d 1331, 1336 (Fed. Cir. 2006) (stating that a person of ordinary skill possesses the “understandings and knowledge reflected in the prior art”); *see also Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (“[T]he knowledge of [a person of ordinary skill in the art] is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious”). A POSA, based on then existing literature, would also have had general knowledge of the methods used to treat and monitor prostate cancer. (WCK1002, ¶18.)

B. Scope and content of the art before August 25, 2006

Prostate cancer, an androgen-dependent disease, is the second leading cause

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of cancer death among men in the U.S. (WCK1007, 1503; WCK1008, 1241; WCK1002, ¶19.) Androgen steroids activate the androgen receptor (“AR”) on prostate cells, resulting in the transcription of target genes involved in prostate cell proliferation, differentiation, and apoptosis. (WCK1046, 460, Fig. 1; WCK1002, ¶20.) In prostate cancer patients, activation of the AR by androgen steroids also results in the progression and proliferation of the cancer. (WCK1008, 1241; WCK1002, ¶20.) Testosterone and its metabolite dihydrotestosterone (“DHT”) are two important androgens responsible for activating the AR. (WCK1008, 1241; WCK1002, ¶20.)

1. Metastatic castration-resistant prostate cancer

Treatment focusing on targeting prostate cancer through surgical removal of the prostate and local tumors fails in 15-33% of prostate cancer patients and results in metastatic disease. (WCK1008, 1241; WCK1002, ¶¶21-23.) Prostate cancer frequently metastasizes to pelvic lymph nodes and bone, with pain usually being the most significant symptom. (WCK1010, 1756; WCK1002, ¶23.) The first step in treating metastatic disease typically involves orchiectomy (*i.e.*, surgical castration) or administering drugs that decrease androgen production (*i.e.*, chemical castration) (WCK1010, 1756; WCK1002, ¶¶23-26.)

However, it was well-known in the art that peripheral conversion of adrenal steroids to testosterone resulted in as much as 10% of baseline circulating

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androgens remaining in castrate men. (WCK1005, 2317; WCK1009, 548; WCK1002, ¶31.) This extratesticular source of androgens was well-known to be an important alternate source of AR stimulation that can lead to prostate cancer growth despite castrate levels of testosterone. (WCK1005, 2317; WCK1002, ¶31.) Indeed, almost all castrate patients will go on to develop refractory or metastatic castration-resistant prostate cancer (“mCRPC”), *i.e.*, prostate cancer that progresses despite a reduction in androgen levels from surgical or chemical castration.² (WCK1007, 1503; WCK1017, 62; WCK1002, ¶26.)

In addition, the art taught that, after androgen deprivation treatment, prostate tumors evolve mechanisms to reactivate AR signaling and AR-responsive pathways. (WCK1029, 8254; WCK1008, 1242; WCK1002, ¶27.) Preclinical models suggested that low levels of androgens, equivalent to castrate levels, continued to fuel prostate cancer growth. (WCK1008, 1242; WCK1002, ¶27.) Further, it was well-known that the AR could acquire greater sensitivity in mCRPC patients, and thus, could be activated at lower levels of testosterone (WCK1005,

² mCRPC is also widely referred to in the literature as “hormone refractory,”

“hormone resistant,” “androgen resistant,” or “androgen refractory.” (WCK1029, p. 8254; WCK1002, ¶ 26 n.1.) Reference to mCRPC in this petition encompasses these other alternate terms.

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2317; WCK1008, 1242; WCK1002, ¶27.) And inhibiting androgen synthesis through known inhibitors of androgen production, such as ketoconazole and abiraterone acetate, was well-known. (WCK1009, 549; WCK1002, ¶¶36, 38.)

Ultimately, when a patient stopped responding to hormone-focused treatments, cytotoxic agents were usually considered as the next line of treatment. (WCK1009, 549; WCK1002, ¶29.) In 2004, co-administering docetaxel and prednisone was the standard of care for patients who did not respond to androgen deprivation therapy. (WCK1029, 8253; WCK1002, ¶29.) And prior to 2004, the combination of mitoxantrone and prednisone had been the standard chemotherapy regimen for mCRPC. (WCK1007, 1509; WCK1029, 8253; WCK1002, ¶29.) As such, prednisone had been part of the standard of care for mCRPC long before August 25, 2006. (WCK1002, ¶29.)

2. By August 25, 2006, PSA levels were known to be an indicator of prostate cancer progression and tumor burden

Prostate-specific antigen (“PSA”) testing was important in the diagnosis, management, and treatment of hormone refractory prostate cancer, by August 25, 2006. (WCK1004, 1177; WCK1009, 543-544; WCK1018, Abstract; WCK1002, ¶30.) Both nonmalignant and malignant epithelial cells of the prostate produce PSA. (WCK1009, 544; WCK1002, ¶30.) Doctors monitored PSA levels in prostate cancer patients to determine disease progression. (WCK1009, 544, 548-550; WCK1002, ¶30.) A decrease in PSA levels generally correlates with a response to

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treatment, while rising levels correlates with disease progression. (WCK1006, 252; WCK1009, 544, 546-549; WCK1002, ¶30.) Additionally, PSA was a well-known predictor of tumor burden, as well as recurrence and survival. (WCK1018, Abstract; WCK1002, ¶30.)

3. By August 25, 2006, prednisone was known to treat prostate cancer and was co-administered with other anti-cancer agents as part of the standard of care

It was also well-known that glucocorticoids had anti-cancer effects on mCRPC. (WCK1006, Abstract; WCK1011, 544; WCK1017, Abstract; WCK1015, 89-90; WCK1027, 495-496; WCK1002, ¶41.) In fact, practitioners treated various types of cancers with prednisone. (WCK1043, Abstract; WCK1004, Abstract; WCK1045, Abstract; WCK1002, ¶41.) And the art had documented the growth inhibitory effects of glucocorticoids on prostate cancer. (WCK1036, 553; WCK1002, ¶41.) Specifically, both prednisone and hydrocortisone were known to treat prostate cancer before August 25, 2006. (WCK1006, Abstract; WCK1010, Abstract, 1759; WCK1011, 543; WCK1017, 66; WCK1002, ¶¶41-42.)

The art taught that glucocorticoids produce a negative feedback on the pituitary gland, leading to a decrease in both testicular and adrenal androgens. (WCK1036, 553; WCK1037, 648, 650; WCK1002, ¶43.) Indeed, doctors prescribed low-dose corticosteroids with the goal of producing a negative feedback on the pituitary gland to inhibit secretion of adrenocorticotrophic releasing hormone

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(“ACTH”). (WCK1028, Abstract; WCK1002, ¶43.). Inhibiting ACTH secretion leads to a decrease in the synthesis of weak androgens, such androstenedione and dehydroepiandrosterone (DHEA). (WCK1028, 590; WCK1002, ¶43.) These weak androgens can undergo metabolism to produce small amounts of testosterone, which can further exacerbate prostate cancer growth. (WCK1005, 2317; WCK1028, 590; WCK1002, ¶43.) Further, it was suggested that glucocorticoids could “inhibit prostate cancer cell growth by modulating cellular growth factors.” (WCK1036, 553; WCK1002, ¶41.)

In 1998, Sartor reported a $\geq 50\%$ reduction in PSA in 34% of patients dosed with 20 mg/day prednisone. (WCK1006, Abstract, 253-254, Table III; WCK1002, ¶42.) Additionally, the art reported that administering prednisone resulted in a $\geq 50\%$ reduction in PSA in 22% of patients dosed with 10 mg/day prednisone. (WCK1010, 1759; WCK1002, ¶42.) Further, as discussed above, long before August 25, 2006, the combination of mitoxantrone and prednisone was the standard chemotherapy regimen for mCRPC. (WCK1007, 1509; WCK1029, 8253; WCK1002, ¶29.) And in 2004, the standard of care for patients who had progressed on androgen deprivation therapy transitioned to co-administering docetaxel and prednisone. (WCK1029, 8253; WCK1002, ¶29.)

4. Inhibition of CYP17 was known to affect cortisol production and lead to mineralocorticoid excess

As discussed above, it was well known that testosterone and other androgens

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fuel prostate cancer growth. By August 25, 2006, it was also well-known that the CYP17 enzyme has two steroidogenic activities: (1) acting as a 17,20-lyase enzyme that acts to synthesize testosterone precursors, and (2) acting as a 17 α -hydroxylase enzyme that functions in both testosterone and cortisol synthesis. (WCK1009, 2128; WCK1002, ¶33, Fig. 2.)

Cortisol, a member of the glucocorticoid family of steroids, acts in the formation of glucose, cardiovascular function, and the activation of the anti-stress and inflammatory pathways. (WCK1032, 1436; WCK1002, ¶34.) As the body produces more cortisol, a negative feedback on the hypothalamus leads to a reduction in ACTH production. (WCK1033, 294-295; WCK1002, ¶34, Fig. 3.) The reduction in ACTH production consequently reduces the production of cortisol. (WCK1033, 294-295; WCK1002, ¶34, Fig. 3.) By August 25, 2006, it was well-known that when CYP17 activity is inhibited, glucocorticoid production decreases, which interferes with this negative feedback mechanism. (WCK1033, 284; WCK1002, ¶34.) In response, the pituitary gland produces more ACTH to stimulate production of glucocorticoids (*e.g.*, cortisol). (WCK1033, 284; WCK1002, ¶34.)

It was also well-documented that patients with 17 α -hydroxylase deficiency secreted large amounts of the mineralocorticoids 10-deoxycorticosterone and corticosterone without concomitant production of cortisol and other androgens.

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(WCK1009, 2145-2146; WCK1033, 284; WCK1002, ¶¶35, 40.) This excess corticosterone may be further converted to aldosterone, resulting in excess amounts of this mineralocorticoid and a condition called “mineralocorticoid excess.”

(WCK1009, 2128-2129, 2143, 2145-2147; WCK1002, ¶¶35, 40, Fig. 2.)

Mineralocorticoid excess has adverse effects, including hypertension and hypokalemia (reduction in circulating potassium levels). (WCK1009, 2146; WCK1002, ¶35.) It was also well-known that administering a glucocorticoid could relieve mineralocorticoid excess due to CYP17 inhibition. (WCK1011, 544; WCK1040, 814; WCK1009, 2146; WCK1002, ¶¶40, 44.)

5. Ketoconazole and abiraterone acetate were well-known inhibitors of CYP17 by August 25, 2006

By August 25, 2006, ketoconazole was a well-known CYP17 inhibitor. (WCK1035, 2463; WCK1038, Abstract; WCK1030, 24:61-62; WCK1002, ¶36.) Ketoconazole acts to inhibit both the 17 α -hydroxylase and 17,20-lyase activities of CYP17, inhibiting the 17,20-lyase activity more than the 17 α -hydroxylase activity. (WCK1035, 2466, Table I; WCK1038, 1196-1197; WCK1002, ¶37.)

However, ketoconazole had its drawbacks. It was well-known in the art that ketoconazole was an unselective CYP17 inhibitor, weakly and non-selectively inhibiting several cytochrome P450 enzymes. (WCK1004, 1177; WCK1005, 2318; WCK1008, 1242; WCK1012, 542; WCK1002, ¶36). And ketoconazole was well-known to have a blunting or inhibitory effect on cortisol production. (WCK1039,

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732, 735-736; WCK1040, 814-815; WCK1002, ¶37.) Consequently, doctors commonly prescribed ketoconazole off-label (as it was only approved as an anti-fungal agent) in combination with a glucocorticoid, such as prednisone (to inhibit ACTH secretion and prevent mineralocorticoid excess), as a second-line treatment for mCRPC. (WCK1004, Abstract; WCK1005, 2323; WCK1011, 542; WCK1016, 1947; WCK1040, 814; WCK1002, ¶¶37, 44, 45.)

In contrast, abiraterone acetate was known to be a potent and more specific CYP17 inhibitor than ketoconazole. (WCK1005, 2318; WCK1008, 1243-1244; WCK1035, Table 1 (compound 2); WCK1002, ¶39.) Specifically, it was well-known in the art that abiraterone acetate inhibited the 17,20-lyase activity of CYP17 (*i.e.*, the activity that leads to testosterone production (*see* § IV.B.4.)). (WCK1035, Table 1 (compound 2); WCK1030, 22:60-65; WCK1002, ¶38.) Abiraterone acetate also inhibited the 17 α -hydroxylase activity of CYP17 (*i.e.*, the activity that leads to cortisol and testosterone production (*see* § IV.B.4.)), suggesting that, like ketoconazole, administering abiraterone acetate would require co-administering a glucocorticoid, such as prednisone, to prevent mineralocorticoid excess. (WCK1035, Table 1 (compound 2); WCK1030, 22:60-65; WCK1002, ¶¶38.). Indeed, as discussed below, the art reported that abiraterone acetate could inhibit cortisol production. (*See* § IV.C.; WCK1002, ¶¶64, 65.) Abiraterone acetate also reduced testosterone levels more than ketoconazole *in*

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vivo. (WCK1030, 26:32-39, Table 4 (compound 1); WCK1005, 2318; WCK1002, ¶38.)

Petitioner's grounds rely specifically on the following publications:

C. Gerber (WCK1004)

Gerber G.S *et al.*, **“Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic cancer,”** *J. Urol.*, 144:1177-9 (November 1990) (“Gerber”; WCK1004) describes ketoconazole as an inhibitor of gonadal and adrenocortical steroid synthesis. (WCK1004, 1177; WCK1002, ¶70.) Gerber discloses that the cytotoxic effects of ketoconazole on prostate cancer cells *in vitro* are known in the art and investigates its potential role in the treatment of prostate cancer. (WCK1004, 1177; WCK1002, ¶70.)

Gerber teaches co-administering ketoconazole, a known CYP17 enzyme inhibitor, with prednisone in patients with mCRPC. (WCK1004, 1177-1178; WCK1002, ¶61.) Gerber reports administering 600-900 mg/day ketoconazole with 5 mg prednisone twice daily showed that 80% of patients with prostate cancer characterized by progressively increasing prostate specific antigen (“PSA”) levels experienced a decrease in PSA levels in response to treatment. (WCK1004, 1178-1179; WCK1002, ¶61.) Gerber reports that 75% of the patients who had bone pain and/or other symptoms of advancing malignancy at the outset of the study had

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subjective improvement. (WCK1004, 1178; WCK1002, ¶61.) Further, Gerber reports that 20% patients experienced a prolonged (8 to 10 months) favorable response to ketoconazole and prednisone based on persistently decreasing PSA levels and symptomatic improvement, including improvement in bone pain. (WCK1004, 1179; WCK1002, ¶61.)

Gerber discloses that this rate of response is similar to that found in studies that have used changes in “measurable tumor size, bone scan abnormalities, and acid phosphatase to assess response.” (WCK1004, 1179; WCK1002, ¶61.) Gerber concludes that his results demonstrate that some patients with progressive prostate cancer, despite previous hormone therapy, will derive significant benefit from the combination of ketoconazole and glucocorticoid replacement therapy, *e.g.*, by co-administering prednisone. (WCK1004, 1179; WCK1002, ¶61.)

D. O’Donnell (WCK1005)

O’Donnell, A. *et al.*, “**Hormonal impact of the 17 α -hydroxylase/C17-20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer,**” *British J. of Cancer*, 90:2317-25 (2004) (“O’Donnell”; WCK1005) teaches that abiraterone acetate is a CYP17 inhibitor that effectively suppresses testosterone synthesis in patients with prostate cancer. (WCK1005, Abstract; WCK1002, ¶70.) O’Donnell reports that repeated treatment of non-castrate prostate cancer patients with abiraterone acetate at a dose of 800 mg can successfully suppress testosterone

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levels to the castrate range. (WCK1005, Abstract; WCK1002, ¶¶65, 70.)

O'Donnell also teaches that adjusting the dose of abiraterone acetate administered may be needed in order to attain suppression of testosterone levels to target levels. (WCK1005, Abstract, 2324; WCK1002, ¶70.)

O'Donnell also discloses that ketoconazole, too, was a well-known inhibitor of CYP17 that has shown anti-cancer activity for prostate cancer by decreasing the production of adrenal steroids. (WCK1005, 2318; WCK1002, ¶¶38, 70.)

O'Donnell further describes abiraterone acetate as a potent CYP17 inhibitor that is more specific than ketoconazole, and which effectively decreases the production of adrenal steroids. (WCK1005, 2318; WCK1002, ¶¶38, 39, 70.) For instance,

O'Donnell describes the potential utility of abiraterone acetate as an effective anti-cancer agent for treating both castrate and non-castrate patients with advanced prostate cancer. (WCK1005, 2324; WCK1002, ¶70.) Indeed, O'Donnell reports the results of three separate phase I studies in patients with advanced prostate cancer, including patients who had progressed despite prior hormone and anti-androgen therapy. (WCK1005, 2320-2322; WCK1002, ¶¶62-65.) O'Donnell treated patients with various doses of abiraterone acetate, finding that administering 500 and 800 mg/day abiraterone acetate maintained testosterone suppression at target levels. (WCK1005, 2320-2321; WCK1002, ¶¶62-65.)

O'Donnell also suggests that administering abiraterone acetate may cause

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adrenocortical suppression (*i.e.*, suppression of cortisol) that would necessitate concomitant administration of a replacement glucocorticoid. (WCK1005, Abstract; WCK1002, ¶64.) In fact, O'Donnell discloses that patients given abiraterone acetate daily for 12 days had abnormal responses to ACTH stimulation by Day 11. (WCK1005, 2320-2321; WCK1002, ¶¶64-65.) In other words, the patients did not produce cortisol in response to adrenal stimulation. (WCK1002, ¶¶64-65.) A POSA would have understood from this result that abiraterone acetate can inhibit cortisol production, which can lead to mineralocorticoid excess and its resulting side effects that can be treated by replacement glucocorticoids, such as prednisone. (WCK1011, 544; WCK1040, 814; WCK1002, ¶¶35, 64, Fig. 2.)

E. Sartor (WCK1006)

Sartor, O., *et al.*, “**Effect of Prednisone on Prostate-Specific Antigen in Patient with Hormone-Refractory Prostate Cancer**,” *Urology*, 1998 52:252-256 (“Sartor”; WCK1006) reports the results of clinical studies in which patients with mCRPC were administered 20 mg daily of prednisone as a monotherapy. (*See generally* WCK1006; WCK1002, ¶66.) Sartor reports that before his review, only four trials had been published in which PSA levels were monitored to determine the effects of glucocorticoids in patients with mCRPC (WCK1006, 252; WCK1002, ¶77.) To control against confounding variables known to effect PSA, Sartor’s study excluded patients that previously (1) received concomitant treatment

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with radiation therapy, (2) exhibited antiandrogen withdrawal, or (3) received treatment with ketoconazole, suramin, aminoglutethimide, or chemotherapy. (WCK1006, 253; WCK1002, ¶77.) Sartor reports that administering prednisone resulted in a significant decline ($\geq 50\%$) in PSA levels with a duration of response of at least 4 months. (WCK1006, Abstract, 253-254, Table III; WCK1002, ¶¶66, 76.)

F. Summary of the '438 patent

1. Brief description of the '438 patent

Against this background, Auerbach *et al.* filed a patent application directed to methods of treating prostate cancer by co-administering abiraterone and prednisone that issued as the '438 patent on September 2, 2014. The '438 patent asserts its earliest priority claim to August 25, 2006. According to the '438 patent face page, Janssen Oncology, Inc. ("Janssen" or "Patent Owner") owns the '438 patent by assignment. (WCK1001.)

2. The '438 patent claims

The '438 patent has 20 issued claims, 1 independent and 19 dependent. Claim 1, the broadest claim, is reproduced below:

A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone. (WCK1001, 16:16-20.) Claims 2-20 recite dosage amounts for either the

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abiraterone, prednisone, or both, as well as the type of prostate cancer to be treated.

(*Id.*, 16:21-17:14.)

3. Prosecution background and summary of arguments

The '438 patent has a lengthy prosecution. In a first Office Action, all pending claims were rejected for obviousness over O'Donnell (WCK1005) in view of Tannock (WCK1010). The Examiner characterized O'Donnell as disclosing using abiraterone acetate to suppress testosterone levels in prostate cancer patients and Tannock for teaching 10 mg prednisone in combination with the anti-cancer drug mitoxantrone as effective in treating mCRPC. (WCK1031, 73-74.)

In Response, the applicants argued that “nothing in the art teaches or suggests that abiraterone acetate in combination with prednisone would be a particularly useful combination for cancer treatment.” (*Id.*, 85.) The applicants further argued unexpected results based on the disclosure of Sartor 2011 (WCK1042) allegedly showing that abiraterone plus prednisone prolongs overall survival relative to prednisone alone. (WCK1031, 85-86)

The applicants also argued that worldwide sales data for Zytiga[®] (the trade name under which abiraterone acetate is marketed) were evidence of purported commercial success of the claimed invention. (*Id.*, 86.) According to the applicants, sales of Zytiga[®] were evidence of the commercial success of the claimed combination because the approved label for Zytiga[®] directs patients to use

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Zytiga[®] in combination with prednisone. (*Id.*) However, the Examiner maintained the rejection of the claims. (*Id.*, 94-97.)

In Response, the applicants once again argued unexpected results and provided another reference, Ryan 2013 (WCK1023), purporting to show unexpected results of the claimed invention over administering prednisone alone. (WCK1031, 113-114.) Still not persuaded, the Examiner continued to reject the claims. (*Id.*, 119-123.)

Following the Examiner's rejection, the applicants provided the FDA approval label for Zytiga[®] and argued that "taking Zytiga in accordance with the approved label [*i.e.*, in combination with prednisone] represents a commercial embodiment of the presently claimed invention." (*Id.*, 134-135.) The applicants also submitted a news release from the FDA announcing that Zytiga was approved for the additional indication of use in prostate cancer patients prior to receiving chemotherapy. (*Id.*) According to the applications, this was additional evidence of commercial success of the claimed combination. (*Id.*) Additionally, the applicants argued commercial success based on a presentation showing a 70% market share for Zytiga in July 2012 for "chemo refractory prostate cancer patients." (*Id.*) According to the applicants, the presentation showed that, as of April 2013, Zytiga was still the market leader with 57% market share in "chemo-refractory prostate cancer patients," despite another product, Xtandi[®], being introduced in August

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2012. (*Id.*) The applicants argued that “this commercial success [of Zytiga] demonstrates the non-obviousness of the presently claimed invention.” (*Id.*)

In a Notice of Allowance, the Examiner provided the following reason for allowing all pending claims: “The *unexpected commercial success* of the launch of the drug obviates the rejection under 35 USC 103(a).” (*Id.*, 206 (emphasis added).)

V. Claim construction

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations in light of the specification of the ’438 patent. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-2146 (2016). Terms not explicitly discussed below are plain on their face and should be construed to have their ordinary meanings. *See Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1373 (Fed. Cir. 2004).

A. “treat,” “treating,” and “treatment”

The Board has already construed the terms “treat,” “treating,” and “treatment” in *Amerigen Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Paper 14 (PTAB May 31, 2016) to “include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.” For the purposes of this proceeding only, Petitioner analyzes the claims under this construction.

B. “therapeutically effective amount of prednisone”

The Board has already construed the term “therapeutically effective amount

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of prednisone” in *Amerigen Pharms.*, IPR2016-00286, Paper 14 at 6-7, to mean the “an amount of prednisone effective for treating prostate cancer.” For the purposes of the proceeding only, Petitioner analyzes the claims under this construction.

VI. Identification of challenge (37 C.F.R. § 42.104(b))

Wockhardt requests IPR of claims 1-20 of the ’438 patent on the grounds of unpatentability listed in the table below. Per 37 C.F.R. § 42.6(c), copies of the cited prior art references accompany the Petition. In support of the proposed grounds for unpatentability, this Petition is also accompanied by the declaration of Dr. Godley (WCK1002), an expert in the fields of medical oncology and genitourinary cancers, with over 25 years of experience in diagnosing and treating prostate cancer. In addition, this Petition is accompanied by the declaration of Dr. Stoner (WCK1077), and expert in industrial organization, with more than 40 years of experience in antitrust and economics research.

Ground	35 U.S.C. Section (pre-3/16/2013)	Claims	Index of References
1	103(a)	1-20	Gerber (WCK1004), O’Donnell (WCK1005), and Sartor (WCK1006)

This Ground establishes a reasonable likelihood that one or more of the ’438 patent claims are unpatentable. This Ground is also not the same or substantially the same as the Grounds instituted in *Amerigen Pharms.*, IPR2016-00286 (“286 IPR”), Paper 14 for five reasons.

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First, it relies on a different combination of prior art than the 286 IPR, including Sartor (WCK1006), which (1) is not of record in the 286 IPR and (2) was not considered during prosecution of the '438 patent. *Second*, it specifically addresses the Board's construction of "therapeutically effective amount of prednisone." For example, the addition of Sartor teaches that prednisone treats prostate cancer, in accordance with the Board's claim construction in the 286 IPR. Consequently, any consideration of unexpected results shifts from comparison to abiraterone acetate alone to comparison of abiraterone acetate plus prednisone and requires a showing of synergy. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 808-809 (Fed. Cir. 1989). And, as discussed below, there is no evidence to suggest any such synergy. *See* § VI.B.1. As a consequence, there can be not credible claim of unexpected results.

Third, the proffered Ground relies on the declarations of Dr. Godley and Dr. Stoner, which have not been previously considered by the Board and are not duplicative of evidence presented in the 286 IPR. *Fourth*, Wockhardt has not previously challenged the '438 patent and is not a party to the IPR2016-00286 proceedings. *Fifth*, the 286 IPR is still in the beginning stages—no Patent Owner Response has been filed, no final decision has issued, and the parties to that proceeding may settle before a final determination issues.

Indeed, the Board has previously decided not to exercise its discretion under

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§ 325(d) on petitions challenging a patent for which a petition requesting trial had already been filed. For instance, in *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, IPR2016-00408, Paper 9, at 7-8 (PTAB July 7, 2016) the Board granted institution under § 325(d) where, as here, the petitioner was not a party to a previously filed petition and the petition presented testimonial evidence from new declarants.

In *Mastercard Int'l Inc. v. Leon Stambler*, CBM2015-00044, Paper 10, at 11-12 (PTAB July 8, 2015) the Board declined to exercise its discretion under § 325(d) where, again as here, a second petitioner presented a combination of art and arguments not present in a petition previously filed by a different party.

Further, in *Valeo N. Am., Inc. v. Magna Elecs., Inc.*, IPR2014-01206, Paper 13, at 9-12 (PTAB Dec. 23, 2014) the Board declined to deny institution under § 325(d) even where the *identical* petitioner filed a second petition relying on a different combination of prior art already of record in a first petition, as is the case for Gerber and O'Donnell here.

Therefore, as in *Bohringer*, *Mastercard*, and *Valeo*, the Board should not exercise its discretion under § 325(d) to deny institution of this Petition.

A. Ground 1: Claims 1-20 would have been obvious over Gerber, O'Donnell, and Sartor

As supported by the declaration of Dr. Godley, a POSA would have had reason and the know-how to arrive at claims 1-20 in view of Gerber, O'Donnell,

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and Sartor with a reasonable expectation of success. (WCK1002, ¶¶57-105). Each of Gerber, O'Donnell, and Sartor are directed to methods of treating prostate cancer. (*Id.*, ¶¶60-66.) A POSA would have had a reason to modify Gerber's method of administering ketoconazole to use abiraterone acetate, as taught in O'Donnell. (*Id.*, ¶67.) This is because a POSA would have known that abiraterone acetate is a potent and more selective inhibitor of CYP17 than ketoconazole and that abiraterone acetate effectively suppressed testosterone levels in both castrate and non-castrate males. (*Id.*) So, a POSA would have expected abiraterone acetate to be more effective than ketoconazole for treating prostate cancer. (*Id.*)

Additionally, a POSA would have had a reason to maintain co-administration of prednisone, as taught in Gerber, because prednisone was known to treat prostate cancer on its own, as demonstrated by Sartor. (WCK1006, Abstract; WCK1002, ¶68.) Prednisone had been part of the standard of care in prostate cancer treatment long before the '438 patent. (WCK1007, 1509; WCK1029, 8253; WCK1002, ¶68.) And in fact, data from O'Donnell's study indicates that administering abiraterone acetate can inhibit cortisol production, which would require co-administering a glucocorticoid such as prednisone. (WCK1005, 2320-2321; WCK1002, ¶68.)

A POSA would also have had a reasonable expectation of successfully practicing a method of administering abiraterone acetate and prednisone to treat

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prostate cancer. (*Id.*, ¶69.) This is because Gerber discloses that the CYP17 inhibitor ketoconazole in combination with prednisone safely and effectively treats prostate cancer. (WCK1004, 1177-1178; WCK1002, ¶69.) O'Donnell teaches that abiraterone acetate, another CYP17 inhibitor, more specifically inhibits CYP17 and suppresses testosterone levels. (WCK1005, 2318; WCK1002, ¶69.) Sartor teaches that prednisone monotherapy reduces PSA levels, indicating a reduction in tumor burden in prostate cancer patients. (WCK1006, Abstract; WCK1002, ¶69.) And indeed, administering prednisone in combination with other anti-cancer agents had long been part of the standard of care in treating prostate cancer. (WCK1007, 1509; WCK1029, 8253; WCK1002, ¶69.) So, a POSA would have reasonably expected each of abiraterone acetate and prednisone to treat prostate cancer when co-administered. (WCK1002, ¶69.)

1. Claim 1

As shown in the claim chart below, Gerber, O'Donnell, and Sartor together teach every element of claim 1.

Claim 1	Gerber (WCK1004), O'Donnell (WCK1005), and Sartor (WCK1006)
A method for the treatment of a prostate cancer in a human comprising	<p style="text-align: center;"><u>Gerber</u></p> <p>“Ketoconazole ... is a potent inhibitor of gonadal and adrenocortical steroid synthesis. In addition, an in vitro cytotoxic effect on prostate cancer cells was demonstrated. These findings suggested a potential role for ketoconazole in the treatment of prostate cancer.” (WCK1004, 1177) (emphases added).</p>

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Claim 1	Gerber (WCK1004), O'Donnell (WCK1005), and Sartor (WCK1006)
	<p>“A total of 15 patients with hormone refractory metastatic prostate cancer was [sic] treated with ketoconazole and prednisone.” (WCK1004, 1177) (emphasis added).</p> <p>“Therefore, we were prompted to investigate the changes in PSA in men with hormone refractory metastatic prostate cancer treated with a combination of ketoconazole and prednisone.” (WCK1004, 1177) (emphasis added).</p> <p style="text-align: center;"><u>O'Donnell</u></p> <p>“A series of three dose escalating studies were conducted to investigate the ability of the 17α-hydroxylase/C_{17,20}-lyase inhibitor abiraterone acetate, to cause maximum suppression of testosterone synthesis when delivered to castrate and noncastrate males with prostate cancer.” (WCK1005, Abstract)(emphasis added).</p> <p style="text-align: center;"><u>Sartor</u></p> <p>“Data were collected from 29 consecutive patients with hormone-refractory progressive prostate cancer who were treated with 10 mg of prednisone orally two times a day.” (WCK1006, Abstract) (emphasis added).</p>
administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof	<p style="text-align: center;"><u>O'Donnell</u></p> <p>“In all three patients [treated with 500 mg of abiraterone acetate] a reduction in testosterone level of more than 50% from baseline was seen.” (WCK1005, 2320-2321) (emphasis added).</p> <p>“From the repeat doses studies it can be seen that a dose of at least 800 mg is required to maintain testosterone suppression to target levels.” (WCK1005, 2323) (emphasis added).</p> <p>“Repeated treatment of men with intact gonadal</p>

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Claim 1	Gerber (WCK1004), O'Donnell (WCK1005), and Sartor (WCK1006)
	<p>function with abiraterone acetate at a dose of 800 mg can successfully suppress testosterone levels to the castrate range." (WCK1005, Abstract) (emphasis added).</p> <p>"Ketoconazole is relatively unselective, inhibiting both cholesterol side chain cleavage and 11β-hydroxylation ... A direct antitumour effect of ketoconazole <i>in vitro</i> has also been demonstrated." (WCK1005, 2318).</p> <p>"Abiraterone acetate is the 3-acetate and a prodrug form of CB7598 (17-(3-pyridyl)androsta-5,16-dien-3β-ol, abiraterone), a potent inhibitor of the enzyme with a K_{iapp} of 0.5 nM." (WCK1005, 2318).</p> <p>"These studies demonstrate for the first time the potential utility of specific inhibition of 17α-hydroxylase/C_{17,20}-lyase in causing reductions in testosterone levels in both castrate and noncastrate males with prostate cancer. The data indicate that reliably maintaining castrate testosterone levels in intact males in the face of increased levels of LH may require higher doses of abiraterone acetate." (WCK1005, 2324) (emphasis added).</p>
and a therapeutically effective amount of prednisone.	<p style="text-align: center;"><u>Gerber</u></p> <p>"Patients were initially treated with 600 to 900 mg ketoconazole daily in 3 divided doses and 5 mg prednisone twice per day." (WCK1004, 1177-1178) (emphasis added).</p> <p>"In our study 12 of 15 castrated patients (80%) with progressively increasing PSA levels had a decrease in PSA in response to treatment with ketoconazole and prednisone." (WCK1004, 1179).</p> <p>"The mean decrease in PSA in the 12 responding</p>

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Claim 1	Gerber (WCK1004), O'Donnell (WCK1005), and Sartor (WCK1006)
	<p>patients was 49% of the pre-treatment level (mean 312 ng./ml., range 38 to 1,717, before treatment and 138 ng./ml., range 6 to 347, after treatment).” (WCK1004, 1178).</p> <p style="text-align: center;"><u>O'Donnell</u></p> <p>“Adrenocortical suppression may necessitate concomitant administration of replacement glucocorticoid.” (WCK1005, Abstract) (emphasis added).</p> <p>“In the clinical use of both aminoglutethimide and ketoconazole, it is common practice to administer supplementary hydrocortisone and this may prove necessary with 17α-hydroxylase and C_{17,20}-lyase inhibitors such as abiraterone acetate.” (WCK1005, 2323) (emphasis added).</p> <p style="text-align: center;"><u>Sartor</u></p> <p>“In this report, we review our experiences with prednisone 20 mg/day (10 mg two times a day) in patients with progressive prostate cancer despite medical or surgical orchiectomy.” (WCK1006, 253) (emphasis added).</p> <p>“Ten patients (34%) had a PSA decline of more than 50% and 4 patients (14%) had PSA declines of more than 75%. The average and median time for progression-free survivals were 2.8 (95% CI 1.7 to 3.8) and 2.0 (range 0 to 11) months.” (WCK1006, Abstract) (emphasis added).</p>

(a) **Co-administering a CYP17 inhibitor and prednisone to treat prostate cancer was well-known in the art**

Claim 1 requires co-administering a therapeutically effective amount of abiraterone acetate, a CYP17 inhibitor, and prednisone to treat prostate cancer.

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Gerber discloses the results of a clinical study of the CYP17 inhibitor ketoconazole in mCRPC patients. (WCK1004, 1177-1178; WCK1002, ¶71.) Gerber administered patients 600-1200 mg/day ketoconazole and 5 mg of prednisone twice a day. (WCK1004, 1177-1178; WCK1002, ¶71.) Gerber reports that 80% of the patients had a mean decrease in PSA levels of 49%, with a median duration of response to treatment of 3 months. (WCK1004, 1178; WCK1002, ¶71.) Gerber also reports that 20% of patients had a prolonged duration of response of 8 to 10 months, as demonstrated by persistently decreasing PSA levels and symptomatic improvement. (WCK1004, 1178-1179; WCK1002, ¶71.) As discussed in § IV.B.2., doctors routinely monitored PSA levels in prostate cancer patients to determine disease progression, with a decrease in PSA levels—as seen in patients administered ketoconazole—correlating with a response to treatment. (WCK1006, 252; WCK1009, 544, 546-549; WCK1002, ¶71.)

(b) Abiraterone acetate was well-known to be a potent and more specific inhibitor of CYP17 than ketoconazole and to effectively reduce testosterone

Abiraterone acetate was known to be a potent and more specific inhibitor of CYP17 than ketoconazole and it effectively reduced testosterone levels. (WCK1002, ¶72.) For instance, abiraterone acetate was known to more effectively reduced testosterone levels than ketoconazole *in vivo*. (WCK1030, 26:32-39, Table 4 (compound 1); WCK1002, ¶¶38, 72.) Additionally, ketoconazole was known to

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have off target effects, such as reducing the production of the mineralocorticoid corticosterone, due to it inhibiting cytochrome P450 proteins other than CYP17. (WCK1005, 2318; WCK1035, 2467; WCK1002, ¶¶39, 70, 72.) In contrast, studies with abiraterone acetate suggested that it did not inhibit corticosterone production. (WCK1035, 2467; WCK1030, 25:45-48; WCK1002, ¶¶39, 72.)

O'Donnell reports results from clinical studies in castrate and non-castrate males given either 10, 30, 100, 500, or 800 mg abiraterone acetate. (*See generally* WCK1005; WCK1002, ¶73.) O'Donnell discloses that patients who received 500 and 800 mg abiraterone acetate had a significant reduction in testosterone levels. (WCK1005, 2320-2321; WCK1002, ¶73.) Moreover, O'Donnell states his studies demonstrate the potential utility of specifically inhibiting CYP17 to cause reductions in testosterone levels males with prostate cancer. (WCK1005, 2324; WCK1002, ¶73.) O'Donnell also recognizes the importance of abiraterone acetate “in the second-line treatment of patients who have become refractory to gonadotrophin-releasing hormone agonists.” (WCK1005, 2324; WCK1002, ¶73.) So, a POSA would have had a reason to administer abiraterone acetate to a patient with prostate cancer. (WCK1002, ¶74.)

(c) A POSA would have had a reason and the know-how to combine abiraterone and prednisone to treat prostate cancer

A POSA would have had a reason to modify Gerber's co-administration of

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ketoconazole and prednisone to replace ketoconazole with O'Donnell's abiraterone acetate. (*Id.*, ¶75.) This is because, as discussed above, a POSA would have known that abiraterone acetate was a more specific inhibitor of CYP17 than ketoconazole. (*Id.*) Furthermore, O'Donnell teaches that abiraterone acetate effectively reduces testosterone levels in both castrate and non-castrate males. (WCK1005, 2324; WCK1002, ¶75.) A POSA would have wanted to reduce testosterone levels to prevent exacerbation of prostate cancer's growth. (WCK1002, ¶75.)

Additionally, a POSA would have had a reason to maintain Gerber's co-administration of prednisone when administering abiraterone acetate in place of ketoconazole. (*Id.*, ¶¶75-84.) This is because prednisone was known to treat prostate cancer, as well as to offset the side effects from administering a CYP17 inhibitor, such as abiraterone acetate and ketoconazole. (*Id.*)

In fact, Sartor teaches administering 20 mg/day prednisone as a monotherapy in patients with mCRPC. (*See generally* WCK1006; WCK1002, ¶76.) For instance, Sartor reports that 34% of patients studied had a significant decrease in baseline PSA levels, *i.e.*, $\geq 50\%$, with a duration of response of at least 4 months. (WCK1006, 253-254, Table III; WCK1002, ¶76.) As discussed in § IV.B.2., a decrease in PSA levels in prostate cancer patients correlates with a response to treatment. (WCK1006, 252; WCK1009, 544, 546-549; WCK1002, ¶30.) In fact, it was well-known in the art that prostate cancer patients having a

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reduction in baseline PSA levels of greater than or equal to 50%, like those in Sartor, had longer median survival rates. (WCK1025, Abstract; WCK1026, Abstract; WCK1002, ¶78.)

Sartor also teaches that previous studies failed to control for factors that could confound measuring PSA levels. (WCK1006, 252-253; WCK1002, ¶77.) Thus, the therapeutic value of prednisone in treating prostate cancer was unclear before Sartor. (WCK1002, ¶77.) Yet, Sartor excluded patients known to be affected by such confounding factors. (WCK1006, 252-253; WCK1002, ¶77.) From this, Sartor obtained a more normalized population from which any effect on PSA levels, and in turn prostate cancer's response to treatment, could be discerned. (WCK1006, 252-253; WCK1002, ¶77.) So, a POSA reading Sartor would have had a reason to maintain Gerber's co-administration of prednisone when replacing Gerber's ketoconazole with O'Donnell's abiraterone acetate. (WCK1002, ¶78.)

Additionally, a POSA would have known that inhibiting CYP17 can lead to adrenal suppression and mineralocorticoid excess due to increased secretion of ACTH. (WCK1009, 2145, 2146; WCK1033, 284; WCK1002, ¶¶40, 79.) Because of this effect, prednisone was routinely added to ketoconazole administration regimens to reduce the amount of ACTH. (WCK1004, Abstract; WCK1002, ¶¶37, 44, 45.) And, like ketoconazole, abiraterone acetate is a CYP17 inhibitor that disrupts the production of adrenal androgens. (WCK1002, ¶¶36-38, 80.) In fact,

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O'Donnell demonstrates that patients administered abiraterone acetate failed to produce more cortisol in response to ACTH stimulation. (WCK1005, 2321; WCK1002, ¶80.) From this lack of response to ACTH, a POSA would have understood that administering abiraterone acetate could inhibit cortisol production and cause mineralocorticoid excess. (WCK1011, 544; WCK1040, 814; WCK1002, ¶¶35, 64-65, 80, Fig. 2.) Indeed, O'Donnell recognizes this and states that “concomitant administration of replacement glucocorticoid” may be necessary. (WCK1005, Abstract; WCK1002, ¶81.)

So, a POSA would have expected abiraterone acetate, like ketoconazole, to increase ACTH levels and lead to mineralocorticoid excess. (WCK1002, ¶¶44, 81.) Therefore, a POSA would have had a reason to maintain co-administering a glucocorticoid such as prednisone when administering abiraterone acetate. (WCK1002, ¶83.) Moreover, glucocorticoids had been used in prostate cancer treatment as early as the 1950's. (WCK1027, 486-487; WCK1002, ¶82.) Clinicians had long administered prednisone as part of the standard of care: prednisone was a well-known monotherapy treatment (WCK1006, Abstract; WCK1017, Abstract; WCK1028, Abstract; WCK1002, ¶82) and combination therapy treatment (WCK1004, Abstract; WCK1007, Abstract; WCK1010, Abstract; WCK1011, Abstract; WCK1019, Abstract; WCK1002, ¶82).

Therefore, a POSA reading Gerber, O'Donnell, and Sartor would have had a

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reason to co-administer a therapeutically effective amount of prednisone with abiraterone acetate because (1) prednisone was known to treat prostate cancer and (2) prednisone would reduce the side effects of mineralocorticoid excess that could result from abiraterone acetate treatment. (WCK1002, ¶¶83-84.) Thus, prednisone would have served a dual purpose when co-administered with abiraterone acetate. (*Id.*)

(d) A POSA would have had a reasonable expectation of success in practicing the method of claim 1

Also, a POSA would have had reasonably expected to successfully practice a method of treating prostate cancer comprising administering a therapeutically effective amount of abiraterone acetate and a therapeutically effective amount of prednisone. (*Id.*, ¶¶85-86.) This is because Gerber teaches methods of treating prostate cancer safely and effectively using the CYP17 inhibitor ketoconazole. (WCK1004, 1177-1179; WCK1002, ¶¶61, 71, 85.) O'Donnell teaches administering the more selective CYP17 inhibitor abiraterone acetate effectively suppresses testosterone levels—a focus of prostate cancer treatment—in castrate and non-castrate males with prostate cancer. (WCK1005, 2320-2321; WCK1002, ¶85.)

Additionally, a POSA would have had a reasonable expectation that co-administering prednisone would aid in the treatment of prostate cancer. (WCK1002, ¶86.) This is because Sartor discloses that mCRPC patients had a

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signification reduction in PSA levels, *i.e.*, $\geq 50\%$, when administered prednisone as a monotherapy. (WCK1006, Abstract; WCK1002, ¶86.) And a reduction in PSA levels was well-known in the art to be an indicator of a response to prostate cancer treatment. (WCK1025, Abstract; WCK1026, Abstract; WCK1002, ¶¶78, 86.)

Consequently, a POSA would have had a reasonable expectation that co-administering both abiraterone and prednisone would have treated prostate cancer. (WCK1002, ¶86.)

Moreover, O'Donnell's data indicates that patients administered abiraterone acetate for 12 days failed to respond to ACTH stimulation, *i.e.*, they failed to produce more cortisol. (WCK1005, 2321; WCK1002, ¶85.) So, a POSA would have expected that co-administering prednisone would have been necessary to prevent the mineralocorticoid excess that would result from an inhibition of cortisol production. (WCK1011, 544; WCK1040, 814; WCK1002, ¶¶35, 64, 85, Fig.2 .) In fact, a POSA would have known that co-administering prednisone would have decreased production of ACTH. (WCK1028, Abstract; WCK1002, ¶¶86.) And decreased production of ACTH would prevent mineralocorticoid excess, in addition to reducing secretion of androstenedione and DHEAS, which can be converted to testosterone that would further fuel prostate cancer cell growth. (WCK1028, 590; WCK1002, ¶86.)

Therefore, a POSA reading Gerber, O'Donnell, and Sartor would have had a

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reason and the know-how to successfully practice the method of claim 1. And for the reasons outlined above, claim 1 would have been obvious. (WCK1002, ¶¶70-86.)

2. Claims 2 and 3

Claim 2 depends from claim 1 and further requires administering from about 50 mg/day to about 2000 mg/day of abiraterone acetate. Claim 3 depends from claim 2 and further requires administering from about 500 mg/day to about 1500 mg/day abiraterone acetate. O'Donnell teaches administering 500 mg/day or 800 mg/day abiraterone acetate suppress testosterone levels in prostate cancer patients. (WCK1005, 2320-2321; WCK1002, ¶88.) Both 500 mg/day and 800 mg/day fall within the ranges recited in claims 2 and 3. As such, in addition to the reasons outlined above for claim 1, claims 2 and 3 would have been obvious. *See In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (“[I]t is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification.”); *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) (stating that a claim to a genus of subject matter necessarily encompasses all of the species that fall within that genus, and so can be invalid over the disclosure of even a single species in the prior art).

3. Claim 4

Claim 4 depends from claim 3 and further requires administering abiraterone

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acetate in an amount of about 1000 mg/day. O'Donnell discloses administering 200, 500, and 800 mg/day of abiraterone acetate. (WCK1005, 2320-2321; WCK1002, ¶89.) However, O'Donnell also discloses that the dose of abiraterone acetate may need to be increased to reliably maintain sufficient suppression of testosterone production in some patients. (WCK1005, 2324; WCK1002, ¶89.)

For instance, O'Donnell reports that administering 200 mg/day or less of abiraterone acetate did not produce a measurable reduction in testosterone levels. (WCK1005, 2320-2321; WCK1002, ¶89.) In contrast, administering 500 or 800 mg/day produced a more profound response. (WCK1005, 2320-2321; WCK1002, ¶89.) Thus, the amount of abiraterone acetate administered is a result-effective variable. So, a POSA would have had a reason to optimize the amount of abiraterone acetate administered to a patient because it would affect the extent testosterone levels would have been reduced in in a patient. (WCK1005, 2320-2321; WCK1002, ¶89-90.) Furthermore, there is no indication in the '438 patent that the claimed concentration is critical. (WCK1002, ¶89.) And it would have been well within the technical grasp of a POSA to optimize dosage amounts and dosing regimens to balance efficacy and toxicity by August 25, 2006. (WCK1032, 65-69; WCK1002, ¶90.)

As such, in addition to the reasons outlined above for claims 1 and 3, a POSA would have arrived at the method of claim 4 with a reasonable expectation

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of success through routine optimization. *In re Aller*, 220 F.2d at 456 (“where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation,” especially if such conditions are not “critical”); *Biocraft Labs., Inc.*, 874 F.2d at 807-809 (finding obvious composition claims to specific ratios of two prior art compounds with known properties when the claimed composition was used for the identical purpose taught in the prior art and a POSA would have arrived at the claimed ratios by routine experimentation).

4. Claim 5

Claim 5 depends from claim 1 and further requires that the abiraterone acetate is administered in at least one 250 mg dosage form. O’Donnell administered abiraterone acetate capsules containing 10, 50, 100, and 200 mg abiraterone acetate. (WCK1005, 2319; WCK1002, ¶91.) As discussed above for claim 4, a POSA would have had a reason to optimize the daily dosage of abiraterone acetate to 1000 mg/day. A POSA also would have known that patient compliance should be considered when developing a pharmaceutical dosage form. (WCK1041, 1705-1706; WCK1002, ¶91.) As such, a POSA would have been motivated to optimize the dosing regimen to administer the fewest number of capsules or tablets per day. (WCK1041, 1705-1706; WCK1002, ¶91.) Furthermore, it would have been well within the technical grasp of a POSA to

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modify O'Donnell's 200 mg capsules to make a 250 mg capsule. (*See generally* WCK1041, 1553-1584; WCK1002, ¶91.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reasonable expectation of success in arriving at the method of claim 5. *In re Aller*, 220 F.2d at 456 (“[I]t is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification ... changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result”). *Cf. Tyco Healthcare Grp. LP v. Mut. Pharm. Co., Inc.*, 642 F.3d 1370, 1372-1732 (Fed. Cir. 2011) (finding claims to a 7.5 mg capsule obvious prior art capsules containing 15 mg and 30 mg combined with a teaching of dosing 5 mg to 15 mg).

5. Claims 6-8

Claim 6 depends from claim 1 and further requires administering from about 0.01 to about 500 mg/day prednisone. Claim 7 depends from claim 6 and further requires administering from about 10 to about 250 mg/ day prednisone. Claim 8 depends from claim 7 and further requires administering about 10 mg/day prednisone.

Sartor discloses administering 20 mg/day prednisone as a monotherapy is safe and effective for treating prostate cancer. (WCK1006, 253; WCK1002, ¶92.) Gerber discloses administering 10 mg/day prednisone in combination with the CYP17 inhibitor ketoconazole is safe and effective for treating prostate cancer.

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(WCK1004, 1178; WCK1002, ¶92.) Each of 10 and 20 mg/day prednisone falls within the ranges recited within claims 6 and 7. As such, in addition to the reasons outlined above for claim 1, claims 6 and 7 would have been obvious. *In re Aller*, 220 F.2d at 456; *Atlas Powder*, 190 F.3d at 1346.

In addition, a POSA would have known that prolonged therapy with corticosteroids, such as prednisone, may result in negative side effects, such as fluid and electrolyte disturbances, hypertension (*i.e.*, high blood pressure), hyperglycemia (*i.e.*, high blood sugar), peptic ulcers, myopathy, and a host of other issues. (WCK1032, 1448, 1451-1452; WCK1002, ¶93.) And in fact, Sartor reports that several patients in his study developed proximal muscle weakness indicative of steroid-induced myopathy and one patient developed diabetes. (WCK1006, 254; WCK1002, ¶93.)

Consequently, a POSA would have had a reason to optimize the amount of prednisone administered to treat prostate cancer because it would be a result-effective variable that would affect the chances a patient would develop undesirable side effects. (WCK1002, ¶93.) Furthermore, there is no indication in the '438 patent that the claimed dosage amount is critical. (*Id.*) And it would have been well within the technical grasp of a POSA to optimize the dosage amount of prednisone to have the greatest efficacy with the fewest side effects when co-administering another agent for treating prostate cancer. (WCK1032, 65-69;

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WCK1041, 1706; WCK1002, ¶94.) Moreover, a POSA reading Gerber would have recognized that adjusting the dose of prednisone to 10 mg/day was safe and effective when co-administering a CYP17, such as ketoconazole or abiraterone acetate. (WCK1004, 1177-1178; WCK1002, ¶94.) So, in addition to the reasons outlined above for claims 1 and 7, claim 8 would have been obvious. *In re Aller*, 220 F.2d at 456; *Biocraft Labs.*, 874 F.2d at 807-809.

6. Claim 9

Claim 9 depends from claim 1 and further requires administering prednisone in at least one dosage form comprising about 5 mg. Gerber teaches administering a single dosage form containing 5 mg prednisone twice daily in combination with a CYP17 inhibitor for treating prostate cancer (WCK1004, 1178; WCK1002, ¶95.) So, in addition for the reasons outlined above for claim 1, claim 9 would have been obvious.

7. Claims 10 and 11

Claim 10 depends from claim 1 and further requires administering about 500 to about 1500 mg/day abiraterone acetate and about 0.01 to about 500 mg/day of prednisone. Claim 11 depends from claim 10 and further requires administering about 1000 mg/day abiraterone acetate and about 10 mg/day of prednisone.

As discussed above, O'Donnell teaches administering 500 or 800 mg/day abiraterone acetate effectively suppresses testosterone levels in patients with

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prostate cancer. (WCK1005, 2321-2323; WCK1002, ¶96.) In addition, Gerber and Sartor disclose administering 10 and 20 mg/day prednisone, respectively.

(WCK1004, 1178; WCK1006, 253; WCK1002, ¶96.) And Gerber teaches administering 10 mg/day prednisone in combination with a CYP17 inhibitor.

(WCK1005, 1178; WCK1002, ¶96.) These amounts of abiraterone acetate and prednisone fall within the recited range of claim 10. As such, in addition to the reasons outlined above for claim 1, claim 10 would have been obvious. *In re Aller*, 220 F.2d at 456; *Atlas Powder*, 190 F.3d at 1346; *Biocraft Labs.*, 874 F.2d 804, 807 (finding obvious composition claims to specific ratios of two prior art compounds with known properties when the claimed composition was used for the identical purpose taught in the prior).

And as discussed above for claims 4, 7, and 8, a POSA would have had a reason to optimize the doses of abiraterone acetate and prednisone administered to be about 1000 mg/day and 10 mg/day, and would have done so successfully. *See* §§ VI.A.4 and VI.A.5. (WCK1002, ¶¶97-98.) As such, in addition to the reasons outlined above for claims 1 and 10, claim 11 would have been obvious. *In re Aller*, 220 F.2d at 456; *Biocraft Labs.*, 874 F.2d at 807-809.

8. Claims 12 and 13

Claim 12 depends from claim 1 and further requires that the prostate cancer is refractory prostate cancer. Claim 13 depends from claim 12 and further requires

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that the refractory prostate cancer is not responding to at least one anti-cancer agent. O'Donnell reports the results of phase I clinical trials in patients classified as having stable recurrent malignancy (WCK1005, Abstract, 2319-2321.) This means that the patient's cancer had progressed despite previous anti-cancer therapy. (WCK1002, ¶99.)

A cohort of patients in O'Donnell's study previously received treatment with at least one anti-cancer agent, *i.e.*, an anti-androgen and a gonadotropin-releasing hormone ("GnRH") agonist. (WCK1005, 2320; WCK1002, ¶99.) So, in addition to the reasons outline for claim 1 above, claims 12 and 13 would have been obvious because O'Donnell teaches that abiraterone acetate is effective for treating patients with mCRPC that are not responding to at least one anti-cancer agent, *i.e.*, patients with refractory prostate cancer. (WCK1002, ¶99.)

9. Claims 14-16

Claim 14 depends from claim 13 and further requires that the at least one anti-cancer agent comprises a hormonal ablation agent, an anti-androgen agent, or an anti-neoplastic agent. Claim 15 depends from claim 14 and further requires that the hormonal ablation agent comprises deslorin, leuprolide, goserelin, or triptorelin. Claim 16 depends from claim 14 and further requires that the anti-androgen agent comprises bicalutamide, flutamide, or nilutamide.

As discussed above, a cohort of patients in O'Donnell's study previously

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received at least one anti-cancer agent, specifically either an anti-androgen or a hormonal ablation agent, as recited in claim 14. (WCK1005, 2320; WCK1002, ¶61, 101.) For example, O'Donnell discloses that the patients in "Study A" had received flutamide, as recited in claim 16. (WCK1005, 2320; WCK1002, ¶101.) Additionally, the patients received leuprolide or goserelin, as recited in claim 15. (WCK1005, 2320; WCK1002, ¶101.) So, in addition to the reasons outline above for claims 1 and 13, claims 14-16 would have been obvious.

10. Claim 17

Claim 17 depends from claim 14 and further requires that the anti-neoplastic agent comprises docetaxel. Although O'Donnell does not expressly disclose administering abiraterone acetate to a patient who has become refractory to docetaxel, by August 25, 2006, docetaxel was a well-known anti-neoplastic agent that had been co-administered as with prednisone as an FDA approved for metastatic prostate cancer. (WCK1007, Abstract; WCK1002, ¶102.) It was known that Docetaxel and abiraterone acetate each treat prostate cancer through different mechanisms of action: docetaxel reversibly binds to microtubules and prevents cell division, while abiraterone acetate inhibits CYP17 and decreases testosterone production. (WCK1034, 6; WCK1005, Abstract; WCK1002, ¶102.) So, a POSA would have had a reason to treat a patient who had progressed after docetaxel treatment with a different anti-cancer regimen that has a different mechanism of

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action, such as abiraterone acetate. (WCK1002, ¶102.)

As such, a POSA would have had a reasonable expectation of success that co-administering abiraterone acetate with prednisone would have been effective in treating patients not responding to docetaxel because (1) O'Donnell discloses that abiraterone acetate is effective in treating prostate cancer patients whom had become refractory to at least one anti-cancer agent and (2) docetaxel and abiraterone acetate have different mechanisms of action in treating cancer. (WCK1002, ¶102.)

11. Claims 18-20

Claim 18 depends from claim 12 and further requires administering about 500 to about 1500 mg/day of abiraterone acetate and about 0.01 to about 500 mg/day abiraterone acetate. Claims 19 and 20 depend from claims 18 and 17, respectively and further require administering about 1000 mg/day abiraterone acetate and about 10 mg/day prednisone.

As discussed above for claim 10, a POSA would have arrived at a method of administering about 500 to about 1500 mg/day of abiraterone acetate and about 0.01 to about 500 mg/day abiraterone acetate with a reasonable expectation of success. *See* § VI.A.7.; *In re Aller*, 220 F.2d at 456; *Atlas Powder*, 190 F.3d at 1346. And as discussed above for claim 11, a POSA would have arrived at a method of administering about 1000 mg/day abiraterone acetate and about 10

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mg/day prednisone. *See* § VI.A.7.; *In re Aller*, 220 F.2d at 456; *Biocraft Labs.*, 874 F.2d at 807-809.

So, in addition to the reasons outlined for claims 1, 10, and 12, claim 18 would have been obvious. *See* §§ VI.A.7. and VI.A.8. This is because O'Donnell teaches administering 500 mg/day and 800 mg/day abiraterone acetate was effective in treating prostate cancer in patients with refractory prostate cancer that are not responding to at least one anti-cancer agent. (WCK1005, 2321-2323; WCK1002, ¶103.)

And in addition to the reasons outlined above for claims 1, 11, 12, 17, and 18, claims 19 and 20 would have been obvious. *See* §§ VI.A.7., VI.A.8, and VI.A.10. This is because O'Donnell teaches that administering 500 and 800 mg/day abiraterone acetate was effective in treating prostate cancer in patients with refractory prostate cancer that are not responding to at least one anti-cancer agent. (WCK1005, 2321-2323; WCK1002, ¶¶96, 103.) Moreover, O'Donnell teaches that doses greater than 800 mg/day, *e.g.*, 1000 mg/day, may be necessary to reliably maintain sufficient suppression of testosterone production in some patients, such those with refractory prostate cancer who were the subjects of O'Donnell's study. (WCK1005, 2324; WCK1002, ¶¶94, 104-105.)

B. Objective indicia of nonobviousness do not weigh in favor of patentability of claims 1-20

In addition to Wockhardt's strong showing of *prima facie* obviousness,

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objective indicia must be taken into account, although it does not control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (finding that before the Board consideration of objective indicia is part of the whole obviousness analysis, not just an afterthought). However, where a strong showing of *prima facie* obviousness exists, the Federal Circuit has repeatedly held that even relevant secondary considerations supported by substantial evidence is still insufficient to overcome obviousness. *See, e.g., Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Objective evidence must be attributable to the claimed invention, and apart from what is unclaimed or in the prior art. *See In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011); *see also Gnosis S.p.A. v. Merck & Cie*, IPR2013-00117, Paper 71, at 35 (PTAB June 20, 2014) (“Based on evidence before us, we are not persuaded that ‘the objective indicia of non-obviousness [is] tied to the novel elements of the claim at issue’ in this case ... As such, insufficient nexus exists.”); *Medtronic, Inc. v. Martial Deduction Trust*, IPR2014-00100, Paper 46, at 28 (PTAB Mar. 24, 2015) (“[N]o evidence of record indicates that a nexus exists between the sales of the mentioned devices and novel or non-obvious aspects of the subject matter recited in the challenged claims.”).

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And lastly, “[e]vidence of secondary considerations must be reasonably commensurate with the scope of the claims.” *In re Kao*, 639 F.3d at 1068; *see also Gnosis S.p.A.*, IPR2013-00117, at 38-39 (finding that that the patent owner’s contentions regarding unexpected results were not commensurate in scope with the claims at issue).

Patent Owner may argue that secondary considerations of commercial success, long-felt but unmet need, failure of others, or unexpected superior results exist.

1. No unexpected superior results

Janssen argued unexpected results during prosecution of the ’438 patent and in its Preliminary Patent Owner Response in *Amerigen Pharms.*, IPR2016-00286, Paper 12, at 11-16 (“286 POPR”). But as discussed below, these arguments fail and do not support patentability.

(a) Unexpected results raised during prosecution do not weigh in favor of patentability

During prosecution, the applicants argued unexpected results based on a comparison of abiraterone acetate and prednisone versus prednisone alone. This comparison is wrong. (WCK1002, ¶116.) Although prednisone was known to have a modest anti-cancer effect on hormone refractory prostate cancer (*see, e.g.,* WCK1006, Abstract), as Dr. Godley explains, a POSA likely would not have administered prednisone alone to treat prostate cancer, except for palliative

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treatment in patients who had progressed on all other available treatments.

(WCK1002, ¶116.) Moreover, it was well-known in the art that abiraterone acetate was an inhibitor of CYP17, which would result in a suppression of testosterone production. (*See* § V.A.) As such, a POSA would have expected that co-administering abiraterone acetate and prednisone would have been more effective in treating cancer than prednisone alone. (WCK1002, ¶116.) And because administering each of abiraterone acetate and prednisone were known for treating prostate cancer, the appropriate comparison would be to determine if co-administering abiraterone acetate and prednisone produced greater than additive effects. *Biocraft Labs.*, 874 F.2d at 808-809; *In re Huang*, 100 F.3d at 139.

(b) Janssen failed to provide probative evidence of unexpected results in the 286 POPR

In the 286 POPR, Janssen relied on Ryan 2011 (WCK1021) and Attard 2009 (WCK1022) to claim that an unexpected survival benefit was demonstrated in patients treated with abiraterone acetate and prednisone (Ryan 2011) versus abiraterone alone (Attard 2009). (286 POPR at 13-15.) Attard 2009 discloses results of a phase I/II clinical trial in which patients with mCRPC were given abiraterone acetate. Patients in this study who progressed were given dexamethasone in addition to the abiraterone acetate. (WCK1022, 3743). Ryan 2011 discloses results of a phase II clinical trial in which patients with mCRPC were given a combination of abiraterone acetate and prednisone. (WCK1021,

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4855). But this data does not, and indeed cannot, demonstrate any unexpected result that weighs in favor of patentability.

i. The proffered evidence does not show unexpected results

First, a comparison of clinical data across disparate patient populations is not clinically sound. (WCK1002, ¶111.) Therefore, Janssen's analysis starts from a flawed foundation and cannot credibly show any unexpected result. (*Id.*)

Second, a showing of unexpected results from co-administering abiraterone acetate and prednisone should provide a synergistic and not just an additive effect in treating prostate cancer. *Biocraft Labs.*, 874 F.2d at 808-809 (“Given the prior art teaching that both [compounds] are natriuretic, it is to be expected that their co-administration would induce more sodium excretion than would either diuretic alone.”) (citing *In re Crockett*, 279 F.2d 274, 276 (CCPA 1960)); *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). Yet, even if one were to compare the results of the two trials, the comparison between Ryan 2011 and Attard 2009 does not demonstrate a synergistic effect on the survival benefit from co-administering abiraterone acetate and prednisone. (WCK1002, ¶¶110-115.)

Third, the results from comparing Ryan 2011 and Attard 2009 would not have been unexpected due to factors unrelated to therapeutic regimens. (*Id.*, ¶110-115.) This is because the patients in Attard 2009 had much more advanced disease than those in Ryan 2011. (*Id.*) Consequently, a POSA would have expected that the

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patients in Ryan 2011 would have responded better to treatment with abiraterone acetate, whether or not prednisone was present. (*Id.*)

For example, Janssen compares the survival rates between patients in Attard 2009 and Ryan 2011 to demonstrate evidence of unexpected results, yet the Ryan 2011 study states that, “[t]he PSA response proportion of 67% in this study is slightly higher than that observed in previous phase II studies with abiraterone acetate.” (WCK1021, 4860; WCK1002, ¶110.) As Dr. Godley explains, multiple explanations for this observation may exist, but most importantly the population in Ryan 2011 had much less extensive disease than those in Attard 2009—as demonstrated by the disparate values in the median PSA level of the patients in each study (*i.e.*, the Ryan 2011 patients had a median PSA level of 23, while the Attard 2009 patients had a median PSA level of 110). (WCK1002, ¶110; WCK1021, Table 1; WCK1022, Table 1.) Consequently, as Dr. Godley explains, any decrease in PSA levels was most likely not because of co-administering prednisone with abiraterone acetate versus administering abiraterone alone. (WCK1002, ¶110-115.) But instead, it is a reflection of treating a patient population with less extensive disease, *i.e.*, Ryan 2011’s patients. (*Id.*)

Fourth, as further evidence of the lack of any unexpected results, Dr. Godley explains that Danila (WCK1024) discloses a phase II clinical study in which abiraterone acetate and prednisone were co-administered to patients with mCRPC

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and who had progressed after treatment with docetaxel-based chemotherapy.

(WCK1024, Abstract; WCK1002, ¶¶113-114.) Danila reported that the study's cohort had a median PSA level of 189.6 and a median time to PSA progression ("TTPP") of 169 days. (WCK1024, Abstract, 1497, 1499; WCK1002, ¶¶113-114.)

Danila's reported TTPP was approximately 11 months shorter than the TTPP reported in Ryan 2011. (WCK1024, 1499; WCK1002, ¶113.) This once again demonstrates that the extent of a patient's disease affects the ability of abiraterone acetate and prednisone to affect the length of progression-free survival.

(WCK1002, ¶113-115.)

Based on Danila's data, Dr. Godley concludes, that there is nothing unexpected in Ryan 2011's results. (*Id.*, ¶115.) This is because, like in Attard 2009, the patients in Danila had more extensive disease. (*Id.*) And not surprisingly, the patients in Danila did not respond as well to co-administration of abiraterone and prednisone as did the patients in Ryan 2011, who had much less extensive disease than Danila's patients but received the same treatment as Danila's patients. (*Id.*) Indeed, a POSA would have expected administering two well-known anti-cancer agents would be more effective in treating patients with less extensive disease. (*Id.*, ¶115.) In sum, Janssen failed to put forth any probative evidence of unexpected results in the 286 POPR. (*Id.*, ¶¶108-115.)

Petition for Inter Partes Review of U.S. Patent No. 8,822,438**ii. Janssen's alleged evidence of unexpected results has no nexus to the '438 patent**

Unexpected results must be attributable to the claimed invention, and apart from what is in the prior art, to have a nexus to the claims of the patent. *In re Kao*, 639 F.3d at 1068; *Gnosis S.p.A.*, IPR2013-00117, at 35. Here, both abiraterone acetate and prednisone were both well-known in the prior art before August 25, 2006. Each of abiraterone and prednisone were administered as a monotherapy for treating prostate cancer long before the '438 patent. (*See, e.g.*, WCK1006, Abstract; WCK1005, Abstract; WCK1002, ¶¶38-39, 41-45, 62-66.) Administering prednisone with a CYP17 inhibitor, *i.e.*, ketoconazole, to treat prostate cancer was also well-known long before the '438 patent. (WCK1004, 1177-1178; WCK1002, ¶¶36-37, 60-61.) And co-administering prednisone with other anti-cancer agents, such as docetaxel and mitoxantrone, had long been the standard of care in prostate cancer treatment. (WCK1029, 8253; WCK1007, 1509; WCK1002, ¶29.) Further, dosing information of Jevanta[®] (cabazitaxel), a chemotherapy agent that entered the market a year before Zytiga[®], instructs co-administration with prednisone. (WCK1063, 1; WCK1077, ¶47.) As such, co-administering prednisone with an anti-cancer agent, and even more specifically a CYP17 inhibitor, was already in the prior art and does not defeat a finding of obviousness. *In re Kao*, 639 F.3d at 1068; *Gnosis S.p.A.*, IPR2013-00117, at 35.

Moreover, for there to be a nexus to the '438 patent, the combination of

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abiraterone acetate and prednisone should provide synergistic and not merely additive results. *Biocraft Labs.*, 874 F.2d at 808-809; *In re Huang*, 100 F.3d at 139. But, as discussed above, the comparison of Ryan 2011 to Attard 2009 fails to demonstrate the required synergy. Consequently, Janssen has not demonstrated the required nexus. *In re Kao*, 639 F.3d at 1068; *Gnosis S.p.A.*, IPR2013-00117, at 35.

iii. Janssen's evidence of unexpected results is not commensurate in scope with claims 1-10 and 12-18

The patients in both Ryan 2011 and Attard 2009 received 1000 mg/day abiraterone acetate. (WCK1021, Abstract; WCK1022, Abstract; WCK1002, ¶108.) And Ryan 2011's patients received 10 mg/day prednisone. (WCK1021, Abstract; WCK1002, ¶108.) As such, Janssen's alleged evidence of unexpected results only applies to administering 1000 mg/day abiraterone acetate and 10 mg/day prednisone.

But only claims 11, 19, and 20 specifically recite administering 1000 mg/day abiraterone acetate and 10 mg/day prednisone: claims 1-10 and 12-18 are broader. As such, Janssen's alleged evidence of unexpected results are not reasonably commensurate in scope with claims 1-10 and 12-18, and thus should be ignored for those claims. *In re Kao*, 639 F.3d at 1068; *see also Gnosis S.p.A.*, IPR2013-00117, at 38-39. And even if the Board were to credit Janssen's alleged evidence of unexpected results, which it should not, that evidence does not support patentability of claims 11, 19, and 20.

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2. No commercial success

During prosecution of the '438 patent, the applicants asserted that the commercial success of Zytiga[®], the commercial product containing abiraterone acetate, was evidence of the non-obviousness of the claimed invention.

(WCK1031, 86, 134-135.) And the Examiner allowed the claims based on “[t]he *unexpected commercial success* of the launch of the drug”, Zytiga[®]. (*Id.*, 206 (emphasis added).) But doing so was in error.

Commercial success, is only relevant to an obviousness inquiry if the patentee can show a direct link, or nexus, to the claims of the patent. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006); *Gnosis S.p.A.*, IPR2013-00117, at 35. Moreover, the ability to exclude others from bringing a product to market through either patent-based exclusivities, FDA-based exclusivities, or both makes an inference of nonobviousness from evidence of commercial success weak. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-1377 (Fed. Cir. 2005); *Galderma Labs. v. Tolmar, Inc.*, 737 F.3d 731, 740-741 (Fed. Cir. 2013). Commercial success must arise from the novel features of the claims, not from elements already known in the prior art. *Ormco Corp.*, 463 F.3d at 1313; *Gnosis S.p.A.*, IPR2013-00117, Paper 71 at 35; *Medtronic, Inc.*, IPR2014-00100, Paper 46

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at 28.³

(a) Patent-based and FDA-based exclusivities limit any economic relevance of commercial success

The evidence shows, as discussed in Dr. Stoner’s declaration, that Zytiga[®]’s sales success, if any, derives from a blocking patent— separate from the ’438 patent here—and the New Chemical Entity (“NCE”) FDA regulatory exclusivity, both of which serve to preclude competition resulting in higher sales of Zytiga[®]. (WCK1077, ¶¶36-45.) And neither of these dynamics have any nexus to the ’438 patent. *Teva*, 395 F.3d at 1377; *Galderma*, 737 F.3d at 740-741.

The Federal Circuit’s *Teva* decision controls here and is squarely on point, having nearly identical material facts. In *Teva*, the challenged patent claimed a weekly dosing regimen for the drug alendronate sodium. However, Merck (the patentee) also had another patent that claimed alendronate sodium, which issued

³ The Board should note that Janssen has not established that the sales of Zytiga[®] actually amount to a level that would give rise to a finding of commercial success, as such information is proprietary. (WCK1077, ¶¶63-71.) However, data indicates that Zytiga[®] serves a small patient share and its performance in the marketplace is dwindling. (*Id.*) As such, based on the current record there has been no showing of the substantial sales prong of the commercial success inquiry by Janssen. (*Id.*)

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thirteen years before the patent at issue. 395 F.3d at 1377. And the Court found that this other patent effectively blocked anyone from developing the methods claimed in the challenged patent. *Id.* Likewise, the Court also found that Merck, just like Janssen does here, also enjoyed the right to exclude anyone from marketing an alendronate sodium drug product for five years under the FDA's NCE exclusivity. *Id.* And "[b]ecause market entry by others was precluded on those bases," the Federal Circuit found that an "inference of non-obviousness ... from evidence of commercial success [was] weak." *Id.* The same result should apply here.

Like in *Teva*, Janssen has enjoyed the blocking exclusivity of U.S. Patent No. 5,604,213, which claims the abiraterone compound and methods for treating an androgen-dependent disorders (such as prostate cancer) using abiraterone and abiraterone acetate. (WCK1030; WCK1077, ¶¶23, 37.) The '213 patent issued in 1997, over 19 years ago, and will not expire until December 2016. (WCK1030; WCK1077, ¶37.) Similarly, Janssen has enjoyed five years of marketing NCE exclusivity for abiraterone acetate since April 2011 for Zytiga[®]. (WCK1058, *see* NCE date; WCK1077, ¶12.) These patent and statutory blocks are what's responsible for Zytiga[®]'s sales; not the '438 patent. *Teva*, 395 F.3d at 1377; *Galderma*, 737 F.3d at 740-741. (WCK1077, ¶¶12, 38-39.)

Janssen argued in the 286 POPR that "[i]n 1995, abiraterone acetate was

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licensed, via BTG, to Boehringer, which had abiraterone acetate for four years and failed to arrive at the invention claimed in the '438 patent,” and that “[i]n 1999, after it lost interest in the drug, Boehringer returned the [] license to BTG,” consequently making the drug “available for licensing” from 2000. (286 POPR at 51.) Janssen also claimed that abiraterone “was actively shopped around to other companies” between 2000 and 2004, but there was “limited interest” by the time that Johnson & Johnson “licensed the drug from BTG in 2004,” in view of the fact other companies turned down opportunities to license and commercialize the drug from BTG. (*Id.* at 51-52). Yet Janssen’s arguments lack merit. (WCK1077, ¶¶39-44.)

First, Janssen asserts that only the drug—and not the '213 patent—was licensed. This does not rebut the argument that “blocking patent” activity of the '213 patent limits the relevance of analysis of commercial success as it relates to the '438 Patent. (*Id.*, ¶41.)

Second, Janssen does not elaborate as to whether the license was exclusive or non-exclusive and what “field-of-use” was licensed. (*Id.*, ¶42.) Indeed, an exclusive license would still have prevented third parties from developing the alleged invention claimed in the '438 patent. (*Id.*) Further, Janssen has held exclusive rights in the '213 patent for nearly 20 years since 1997, and will continue until its expiration in December 2016. (*Id.*) Thus, the interest Janssen had in

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licensing the '213 patent does not lessen the impact of the '213 blocking patent on the commercial success analysis.

Third, Janssen fails to support its conclusory statement that Boehringer (the only licensed party) failed to arrive at the '438 patent claims, nor does it substantiate its allegations that abiraterone was available for licensing. (*Id.*, ¶43.) Indeed, Boehringer may have decided not to move forward with the commercialization of abiraterone due to various business factors, and not because of any alleged non-obviousness. (*Id.*) Janssen has not presented any evidence that Boehringer's lack of commercialization was due to a failure to appreciate any potential benefits of combining abiraterone with a prednisone, as the combination of ketoconazole with prednisone was already well-known in the art. (*See* §§ IV.B.5.)

In sum, as in *Teva*, the '213 patent, tied together with Zytiga[®]'s NCE marketing exclusivity, has precluded others from developing the '438 patent's claimed methods. (WCK1077, ¶¶12, 44-45.) Thus, Zytiga[®]'s sales are properly traced to the blocking patent and NCE marketing exclusivity, not the '438 patent. (*Id.*) Therefore, any evidence of commercial success is entitled to little if any weight.

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- (b) There is no nexus between the performance of Zytiga[®] and the '438 patent claims because any features of the '438 patent driving Zytiga[®]'s sales already existed in the prior art**

Janssen has failed to provide any evidence nexus between the Zytiga[®] sales and the '438 patent, either during prosecution or in the 286 POPR. For example, in the 286 POPR Janssen did not address the nexus between the allegedly novel features of the '438 patent and the commercial success of Zytiga[®]. (286 POPR at 49.) Instead, Janssen summarily stated that taking abiraterone acetate with prednisone, as directed by the Zytiga[®] label, is a “commercial embodiment of the claimed invention, erroneously assuming that there are novel features of the '438 patent that drive Zytiga[®]'s commercial success. (*Id.*; WCK1077, ¶33.) To the contrary, several factors demonstrate a lack of nexus between the '438 patent claims and Zytiga[®]'s performance: (1) the '438 patent cannot claim invention of the abiraterone or prednisone compounds themselves; (2) both abiraterone and prednisone were well-known in the prior art, as was administering prednisone with other anti-cancer agents, including CYP17 inhibitors; and (3) the lack of evidence that Zytiga[®]'s sales are driven by the benefits of adding prednisone to the treatment of abiraterone acetate. (*Id.*, ¶¶33-35.)

Janssen cannot show non-obviousness if Zytiga[®]'s alleged commercial success is attributable to characteristics of the claimed method that were already in the prior art. *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007)

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(finding that where commercial success can be attributed to characteristics of the invention that were already in the prior art, non-obviousness is not shown); *Gnosis S.p.A.*, IPR2013-00117, at 35.

As discussed above, methods of using each of abiraterone acetate and prednisone to treat prostate cancer were well-known in the art before the '438 patent. (§§ IV.B.3, IV.B.5., IV.D., IV.E.; WCK1002, ¶¶38-39, 41-45, 82; WCK1077, ¶¶46-53.) Indeed, both abiraterone acetate and prednisone were well-known to have anti-prostate cancer activity when each of them was administered as a monotherapy. (WCK1006, Abstract; WCK1005, Abstract; WCK1002, ¶¶38-39, 41, 82; WCK1077, ¶48.) Moreover, administering prednisone in combination with the CYP17 inhibitor ketoconazole was well-known in the art. (WCK1004, 1177-1178; WCK1002, ¶¶37, 45.) And administering prednisone with other anti-cancer agents, such as docetaxel and mitoxantrone, had long been the standard of care in prostate cancer treatment. (WCK1029, 8253; WCK1007, 1509; WCK1002, ¶29.) Further, dosing information of Jevanta[®] (cabazitaxel), a chemotherapy agent that entered the market a year before Zytiga[®], instructs co-administration with prednisone. (WCK1049; WCK1077, ¶47.)

As such, co-administering prednisone with another anti-cancer agent when treating prostate cancer was already in the prior art and does not defeat a finding of obviousness. *Dippin' Dots*, 476 F.3d at 1345; *Gnosis S.p.A.*, IPR2013-00117, at

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35. Consequently, no nexus between the commercial success of Zytiga[®] and the '438 patent claims exists. (WCK1077, ¶¶46-53.)

Further, no available evidence suggests that Zytiga[®] sales are due to the benefits of co-administering prednisone with abiraterone acetate, or a synergistic effect of administering abiraterone and prednisone, rather than the additive benefits of each component individually. (WCK1077, ¶¶50-53.) Indeed, the expansion of Zytiga[®]'s label to include an indication for treating pre-chemo patients due to data that "showed that Zytiga plus prednisone provides a statistically significant [overall survival] benefit vs. prednisone alone" failed to have any market effect. (*Id.*, ¶35.) Consequently, the addition of prednisone to the administration of abiraterone adds nothing substantial over the administration of abiraterone acetate alone and what was already in the prior art. (*Id.*, ¶¶35, 50-53.)

(c) Xtandi[®] has taken Zytiga[®]'s market share

Because of the known side effects of long-term prednisone administration, the need to combine abiraterone with prednisone has become a drawback of Zytiga[®]. (WCK1065; WCK1077, ¶54.) As a result, Zytiga[®] has lost market share to more recently-introduced prostate cancer drugs, such as Xtandi[®] (enzulutamide), which do not require co-administration with a steroid. (WCK1065; WCK1077, ¶54.) Competition from Xtandi[®] has also resulted in (1) lowering of Zytiga[®]'s price, (2) industry expectations that Xtandi[®] will become the premier treatment

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option, and (3) Janssen's investment in a competitor to Xtandi[®]. (WCK1077, ¶¶54-58) This market shift is particularly notable in light of the applicants' argument during prosecution that Zytiga[®]'s continued commercial success after the introduction of Xtandi[®] was further evidence of the commercial success of the invention. (*Id.*, 67.)

(d) Unexpected commercial success of Zytiga[®] is neither economically nor legally relevant, and the performance metrics for Zytiga[®] presented during prosecution of the '438 patent are misleading and incomplete

In allowing the '438 patent, the Examiner cited to the "unexpected commercial success" of the launch of Zytiga[®] as overcoming the pending obviousness rejections. (WCK1031, 206.) Yet, "unexpected" commercial success has no bearing on a finding of nonobviousness based on commercial success because it would not affect the material economic incentives for development that existed at the time of the alleged invention of the '438 patent. (WCK1077, ¶59.)

If the claim is that there was "unexpected" commercial success based on "unexpected" Zytiga[®] sales in relation to what would have been predicted based on the known effects of abiraterone acetate and prednisone in the prior art, no evidence in the record supports such a conclusion. (*Id.*, ¶60.) Indeed, as discussed in § VI.B.2(b), any features of the '438 patent that drove Zytiga[®]'s sales were already present in the prior art. (*Id.*)

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Moreover, the '438 patent applicants did not provide the Examiner with any expectations or perceptions of expected commercial success of Zytiga[®]. (*Id.*, ¶61.) In fact, they only provided to the Examiner post-launch data based on an erroneous patient-share and relative to other oral cancer drugs, which was misleading and incomplete. (*Id.*) But, any success of Zytiga[®] would have been expected, not based on any alleged patentable features of the '438 patent, but based on the prior knowledge of the anti-cancer effect of each of abiraterone and prednisone individually. (*Id.*, ¶¶61-62.) As such, any claims of “unexpected” commercial success by Janssen should be ignored.

3. No long felt need and failure of others

A showing of a long-felt and unmet need requires that the need must have been a persistent one that was recognized by those of ordinary skill in the art. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). The long-felt need must not have been satisfied by another before the invention. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d 1559, 1574-75 (Fed. Cir. 1992). The invention must in fact satisfy the long-felt need. *Id.* at 1575. Failure of others to find a solution to the problem which the patent purports to solve is also relevant in determining nonobviousness. *Id.*

As discussed in §§ IV.B. and VI.A., administering abiraterone acetate and prednisone both individually for treating prostate cancer was well-known in the art

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by August 25, 2006. (*See, e.g.*, WCK1005, Abstract; WCK1006, Abstract; WCK1002, ¶¶38-39, 41-45, 62-66.) Moreover, co-administering abiraterone acetate and prednisone did not provide any unexpectedly superior results for treating prostate cancer. (*See* §VI.B.1.) Further, co-administering prednisone with abiraterone acetate did not satisfy any need to make abiraterone acetate significantly more effective in prolonging progression-free survival. (WCK1002, ¶118.) Lastly, there was no failure of others to develop a method of treating prostate cancer with abiraterone acetate and prednisone by August 25, 2006. (*Id.*) This is because prednisone had long been the standard of care in prostate cancer treatment and prednisone had already been administered with another CYP17 inhibitor, ketoconazole. (WCK1029, 8253; WCK1007, 1509; WCK1005, 1177-1178; WCK1002, ¶29, 37.)

4. Copying by generic drug makers is irrelevant

Janssen may argue that Wockhardt and other generic drug companies seek to copy the invention of the '438 Patent by commercializing generic versions of abiraterone acetate. Because copying “is required for FDA approval” of generic drugs, any “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

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VII. Conclusion

Each of claims 1-20 is obvious over the asserted prior art as discussed above for the reasons stated in Ground 1. Thus, the Board should institute IPR for each challenged claim.

VIII. Mandatory notices (37 C.F.R. § 42.8)

Real Parties-In-Interest (37 C.F.R. § 42.8(b)(1)): Wockhardt Bio AG, Wockhardt Limited, Wockhardt USA LLC, Morton Grove Pharmaceuticals, Inc., and MGP Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)):

Administrative: *Amerigen Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286 (PTAB Dec. 4, 2015); *Argentum Pharms. LLC v. Janssen Oncology, Inc.*, IPR2016-01317 (PTAB June 29, 2016); *Mylan Pharms. Inc. v. Janssen Oncology, Inc.*, IPR2016-01332 (PTAB June 30, 2016)

Judicial: *BTG Int'l Ltd. et al. v. Actavis Laboratories FL, Inc., et al.*, 15-cv-5909 (D.N.J.); *Janssen Biotech, Inc. v. Mylan Pharms., Inc. et al.*, 15-cv-130 (N.D.W.V.); *BTG Int'l Ltd. et al. v. Amerigen Pharms., Inc. et al.*, 16-cv-2449 (D.N.J.); *BTG Int'l Ltd. et al. v. Glenmark Pharms. Inc., USA et al.*, 16-cv-3743 (D.N.J.)

Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead counsel: Dennies Varughese (Reg. # 61,868)

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Notice of Service Information (§ 42.8(b)(4)): Please direct all correspondence to lead counsel and back-up counsel at the above address.

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Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed are a Power of Attorney and Exhibit List under 37 C.F.R. § 42.10(b) and § 42.63(e), respectively. The required fee is paid through Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

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Word Count Certification Under 37 C.F.R. § 42.24(a): Petitioner certifies that this Petition is 13,990 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: August 10, 2016

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Petition for Inter Partes Review of U.S. Patent No. 8,822,438

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned “Petition for *Inter Partes* Review of U.S. Patent No. 8,822,438 under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123,” and supporting Exhibits WCK1001 – WCK1080 was served in its entirety on August 10, 2016, upon the following parties via FedEx[®]:

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EXHIBIT G

Castration-Resistant Prostate Cancer: AUA Guideline

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From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Purpose: This Guideline is intended to provide a rational basis for the management of patients with castration-resistant prostate cancer based on currently available published data.

Materials and Methods: A systematic review and meta-analysis of the published literature was conducted using controlled vocabulary supplemented with keywords relating to the relevant concepts of prostate cancer and castration resistance. The search strategy was developed and executed by reference librarians and methodologists to create an evidence report limited to English-language, published peer-reviewed literature. This review yielded 303 articles published from 1996 through 2013 that were used to form a majority of the guideline statements. Clinical Principles and Expert Opinions were used for guideline statements lacking sufficient evidence-based data.

Results: Guideline statements were created to inform clinicians on the appropriate use of observation, androgen-deprivation and antiandrogen therapy, androgen synthesis inhibitors, immunotherapy, radionuclide therapy, systemic chemotherapy, palliative care and bone health. These were based on six index patients developed to represent the most common scenarios encountered in clinical practice.

Conclusions: As a direct result of the significant increase in FDA-approved therapeutic agents for use in patients with metastatic CRPC, clinicians are challenged with a multitude of treatment options and potential sequencing of these agents that, consequently, make clinical decision-making more complex. Given the rapidly evolving nature of this field, this guideline should be used in conjunction with recent systematic literature reviews and an understanding of the individual patient's treatment goals. In all cases, patients' preferences and personal goals should be considered when choosing management strategies.

Key Words: prostatic neoplasms, androgen antagonists, drug therapy, immunotherapy

INTRODUCTION

THE purpose of this guideline is to provide direction to clinicians and patients regarding the management and treatment of castration-resistant prostate cancer. To assist in clinical decision-making, six index cases were developed representing the most common clinical

scenarios that are encountered in clinical practice (see table).

METHODOLOGY

The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on various therapies for CRPC. Guideline

Abbreviations and Acronyms

ADT = androgen deprivation therapy

CRPC = castration-resistant prostate cancer

FDA = Food and Drug Administration

H&P = history and physical

mCRPC = metastatic castration-resistant prostate cancer

OS = overall survival

PFS = progression-free survival

PSA = prostate specific antigen

QOL = quality of life

SRE = skeletal-related event

The complete guideline is available at www.AUAnet.org/education/guidelines/castration-resistant-prostate-cancer.cfm.

This document is being printed as submitted without independent editorial or peer review by the Editors of *The Journal of Urology*®.

Index Patients

Index Patient	Description
Index Patient 1: Asymptomatic non-metastatic CRPC	One of the first clinical presentations of CRPC occurs in a patient with a rising PSA despite medical or surgical castration. This is defined as a patient with a rising PSA and no radiologic evidence of metastatic prostate cancer. The Prostate Cancer Clinical Trials Working Group 2 defines PSA only failure as a rising PSA greater than 2 ng/ml higher than the nadir; the rise has to be at least 25% over nadir confirmed by a second PSA at least three weeks later. The patient is required to have castrate levels of testosterone (less than 50 ng/ml) and no radiographic evidence of metastatic disease.* To date, there are no randomized trials showing an OS benefit in this patient population from a particular form of treatment.
Index Patient 2: Asymptomatic or minimally-symptomatic mCRPC without prior docetaxel chemotherapy	These patients are characterized as having a rising PSA in the setting of castrate levels of testosterone, documented metastatic disease on radiographic imaging and no prior treatment with docetaxel chemotherapy for CRPC. This patient is defined as having no symptoms or mild symptoms attributable to their prostate cancer. In general, if patients require regular narcotic medications for pain relief, they are not included in this category.
Index Patient 3: Symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy	These patients have a rising PSA in the setting of castrate levels of testosterone, documented symptomatic metastatic disease on radiographic imaging and no prior history of docetaxel chemotherapy. The patient must have symptoms that are clearly attributable to the metastatic disease burden, not any other medical condition. If having pain, the patient should require regular opiate pain medications for symptoms attributable to documented metastases in order to achieve an acceptable level of pain control.
Index Patient 4: Symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy	Clinical trials have generally excluded patients with a poor performance status from participation. Thus, most data regarding management of such patients is extrapolated from randomized trials of eligible patients who had a better performance status; however, treatments with acceptable safety profiles do exist and should be considered. This is especially true in those patients in whom the poor performance status may be considered directly related to the cancer itself, and thus whose status might improve with effective treatment.
Index Patient 5: Symptomatic mCRPC with good performance status and prior docetaxel chemotherapy	As patients with prostate cancer receive hormonal therapy earlier in the course of the disease, they may actually develop non-metastatic or asymptomatic castration-resistant disease resulting in a population of mCRPC patients who have completed docetaxel and may continue to be asymptomatic or minimally symptomatic with an excellent performance status. A focus of therapy should be to maintain their excellent performance status without significant toxicity from additional therapy.
Index Patient 6: Symptomatic mCRPC with poor performance status and prior docetaxel chemotherapy	The American Society of Clinical Oncology advocates for an increasing emphasis on a patient's quality of life and concentrates on symptom management. Treatment given in the last months of life may delay access to end of life care, increase costs and add unnecessary symptom management. Patients with poor performance status (ECOG 3 or 4) should not be offered further treatment.

* Scher HI, Halabi S, Tannock I et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **26**: 1148.

statements and the accompanying treatment algorithm (see figure) were formed based on this literature review.

The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens.¹ For a complete discussion of the methodology and evidence grading, please refer to the unabridged guideline available at www.AUAnet.org/education/guidelines/castration-resistant-prostate-cancer.cfm.

BACKGROUND

Definition

For the purpose of the guideline, CRPC was defined as a rising prostate specific antigen level and/or radiographic evidence of prostate cancer progression despite medical or surgical castration.

Prevalence

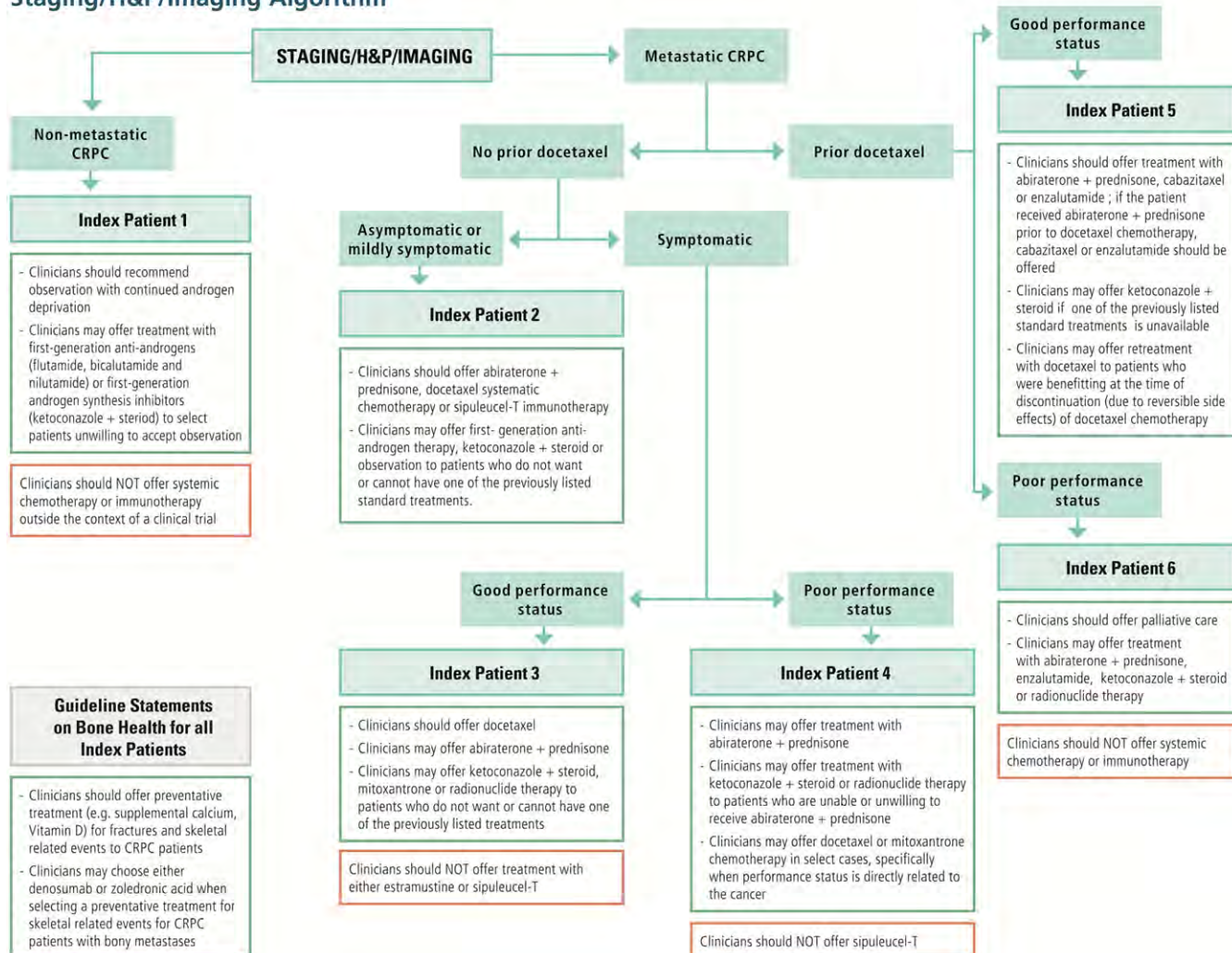
Prostate cancer is the most commonly diagnosed solid organ malignancy in the United States and remains the second leading cause of cancer deaths among men. Approximately 240,000 new diagnoses

of prostate cancer and over 28,000 deaths were estimated in the U.S. in 2012.² While most advanced prostate cancer patients respond initially to androgen deprivation therapy, they ultimately progress despite castration on average between one and three years after initiation of therapy.

Changing Treatment Paradigm

The treatment of men with mCRPC has dramatically changed in the last decade. Prior to 2004, once patients failed primary ADT, treatments were administered solely for palliation. Landmark articles by Tannock et al³ and Petrylak et al⁴ demonstrated that docetaxel improved survival for these patients with mCRPC. Since the approval of docetaxel, four additional agents (enzalutamide, abiraterone, sipuleucel-T and cabazitaxel) that show a survival benefit have been FDA-approved on the basis of randomized clinical trials. These agents have been tested in multiple "disease states" of CRPC to determine if or when patients might benefit from each treatment.

Staging/H&P/Imaging Algorithm



Summary flowchart

GUIDELINE STATEMENTS

Index Patient 1

1. Clinicians should recommend observation with continued ADT to patients with non-metastatic CRPC. (Recommendation; Evidence Level Grade C)

Since all agents have potential side effects, and no treatment has been shown to extend survival or demonstrate a clinically meaningful delay in the development of metastasis, we must first do no harm. As such, it is the Panel's judgment that no treatment (i.e. observation) other than continued ADT be the recommended treatment based upon the lack of any data to refute this recommendation. Patients should be encouraged to enter clinical trials, when available.

2. Clinicians may offer treatment with first-generation antiandrogens (flutamide, bicalutamide and nilutamide) or first-generation androgen

synthesis inhibitors (ketoconazole+steroid) to select patients with non-metastatic CRPC who are unwilling to accept observation. (Option; Evidence Level Grade C)

While it is the Panel's judgment that observation is the most appropriate treatment for this patient population, some patients in this setting may be uncomfortable with treatment with systematic ADT alone and may wish to initiate additional treatment despite the lack of good evidence with regards to the benefits and harms in this setting.

Antiandrogens. Though first-line antiandrogens (flutamide, bicalutamide and nilutamide) are commonly used, these agents can be associated with side effects, including gastrointestinal upset and liver toxicity. Though some small single-arm non-randomized studies suggest a PSA decline,⁵⁻¹⁰ the potential benefit appears modest with PSA declines greater than 50% occurring typically in 20% to 40%

of men with a median duration of only several months. In addition, antiandrogen withdrawal has been used as an option in this setting. There are no randomized studies of either antiandrogens or antiandrogen withdrawal compared to observation; as such, there is a lack of data suggesting any meaningful clinical benefit.

Androgen synthesis inhibitors (ketoconazole). Ketoconazole is a weak inhibitor of CYP11A and CYP17A and suppresses the synthesis of adrenal and tumor tissue androgens. Ketoconazole can be associated with nausea and hepatotoxicity and must be given with replacement steroids. There are multiple single-arm studies that show PSA response rates (greater than 50% decline in PSA) of 30% to 60% with typical responses around 50%.^{11–17}

3. Clinicians should not offer systemic chemotherapy or immunotherapy to patients with non-metastatic CRPC outside the context of a clinical trial. (Recommendation; Evidence Level Grade C)

There are no data to support use of these agents in this patient population. The combination of no known benefit with known and potentially serious harms results in a recommendation not to use these agents.

Index Patient 2

4. Clinicians should offer abiraterone+prednisone, docetaxel or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. [Standard; Evidence Level Grade A (abiraterone)/B (docetaxel)/B (sipuleucel-T)]

Docetaxel chemotherapy and sipuleucel-T immunotherapy are currently the only agents that have demonstrated a survival advantage, while abiraterone+prednisone has demonstrated radiographic progression-free survival benefits. All three have an FDA indication for use in men with mCRPC who have not yet received docetaxel chemotherapy.

Abiraterone. Abiraterone is an irreversible inhibitor of the hydroxylase and lyase activities of CYP17A. Prior to docetaxel chemotherapy, abiraterone+prednisone demonstrated an improvement in radiographic PFS and a trend toward improvement in overall survival in the COU-AA-302 study.¹⁸ Abiraterone is associated with expected increases in mineralocorticoids upstream of CYP17A, accounting for the treatment-related side effects, such as hypertension, hypokalemia, edema and fatigue that respond to low dose glucocorticoids. Use of abiraterone in combination with low dose prednisone is required to prevent these treatment-related increases in

adrenocorticotrophic hormone and attendant side effects.

Docetaxel. Docetaxel is a potent inhibitor of microtubule assembly and disassembly. In a randomized trial of men with mCRPC (TAX-327), patients who received docetaxel+prednisone every three weeks had significantly better survival than those receiving mitoxantrone.³ While this study provides strong evidence to support the use of docetaxel+prednisone in men with mCRPC, there are two important caveats. First, this study did include many patients with symptomatic mCRPC (Index Patient 3). Second, 26% of patients in the docetaxel+prednisone every three weeks arm had one or more serious adverse events, and roughly 11% of patients in this group discontinued treatment due to adverse events. The side effect profile associated with docetaxel may lead patients to delay docetaxel treatment until symptomatic or to elect not to receive this treatment at all. A thorough discussion of the risks and benefits of this treatment is warranted with all patients who are considering this therapy.

Sipuleucel-T. Sipuleucel-T immunotherapy is an FDA-approved agent in this setting based upon the results of the IMPACT trial.¹⁹ In this randomized double-blind placebo controlled clinical trial, men with asymptomatic or minimally symptomatic mCRPC and good functional status treated with sipuleucel-T, as compared to placebo, had a significant reduction in the risk of death. It is worth noting that patients receiving sipuleucel-T therapy rarely (less than 10%) exhibit a clinical, serologic or radiographic response; as such, patients should be counseled appropriately not to expect to see a decline in PSA or reduction in radiological volume of disease when undergoing this treatment.

There are no direct studies comparing the agents that can be used to inform optimal sequencing. As a general principle, it is preferable to give the least toxic agent first, particularly given the lack of head-to-head data, but this must be considered in light of other considerations, including convenience of administration.

5. Clinicians may offer first-generation antiandrogen therapy or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C)

Manipulation with existing antiandrogen agents, such as bicalutamide, nilutamide or flutamide, can only be considered an option in this setting, if only because they offer patients who do not want or cannot have one of the standard therapies a relatively less toxic therapeutic option.

In patients who elect not to receive the standard therapies, there are a number of other options available. Data to support these options in the setting of asymptomatic or minimally symptomatic prostate cancer are limited and generally of lesser strength than the standard treatments. Some have suggested that the removal of antiandrogen therapy may have a beneficial effect on mCRPC. The majority of studies supporting this approach are observational, and the single randomized clinical trial addressing this issue failed to show any survival benefit associated with antiandrogen withdrawal.²⁰

Finally, some patients may not wish to pursue any therapy, waiting for the onset of symptoms to pursue treatment (if they are to ever elect treatment at all). Given current data in this patient population, this approach is a reasonable option.

Index Patient 3

6. Clinicians should offer docetaxel to patients with symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade B)

Docetaxel. As previously noted, high-quality evidence supports the use of first-line docetaxel every three weeks with daily prednisone in symptomatic mCRPC.^{3,4} Bone pain responses were more significant in docetaxel patients (35% vs. 22%, $p = 0.08$), as were improvements in quality of life compared to the mitoxantrone group.

7. Clinicians may offer abiraterone+prednisone to patients with symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Abiraterone+prednisone. In the previously discussed COU-AA-302 study, the Independent Data Monitoring Committee unanimously recommended unblinding based on a planned interim analysis of radiographic PFS, OS and clinical benefit. At 22 months of follow-up, neither median radiographic PFS nor OS for the abiraterone arm had been reached, but the hazard ratio for radiographic PFS was reported as 0.53 (95% CI: 0.45, 0.62) that was statistically significant ($p < 0.001$). OS was improved with abiraterone+prednisone (median survival not yet reached vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93; $p = 0.01$) but did not cross the efficacy boundary.¹⁸ While the randomized phase-III trial was only conducted in asymptomatic and minimally symptomatic men, the mechanism of action of abiraterone is similar to that of ketoconazole and has shown marked palliative and skeletal related benefits. Abiraterone is FDA approved for treatment of this patient population

regardless of symptoms; therefore, it is appropriate for Index Patient 3.

8. Clinicians may offer ketoconazole+steroid, mitoxantrone or radionuclide therapy to patients with symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. [Option; Evidence Level Grade C (ketoconazole)/B (mitoxantrone)/C (radionuclide therapy)]

Ketoconazole. Ketoconazole has not shown significant OS improvements in patients with symptomatic, chemotherapy-naïve mCRPC. Ketoconazole has substantial treatment-related side effects that have prompted the development of more potent CYP17A inhibitors, such as abiraterone.

Mitoxantrone. Mitoxantrone, a microtubule inhibitor, has not shown a survival benefit compared to docetaxel-based chemotherapy regimens in mCRPC as previously discussed.³ Mitoxantrone is primarily utilized in symptomatic mCRPC patients with poor performance status (ie not candidates for docetaxel-based chemotherapy). In support of its use, mitoxantrone has been shown to provide a palliative response in symptomatic patients in one randomized study.²¹

Radionuclide therapy. The use of systemic radiotherapy with samarium-153 or strontium-89 occasionally benefits patients with widely metastatic, symptomatic bone involvement; however, this therapy is usually reserved for candidates who are not responding to palliative chemotherapy and who are not candidates for localized external beam radiotherapy.^{22,23} The risk of bone marrow suppression, which might influence the ability to administer systemic chemotherapy agents, should be considered before initiation of radionuclide therapy.

9. Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Estramustine. Estramustine has both cytotoxic and hormonal effects. The major mechanism of action is as an alkylating agent that has not shown significant OS advantages. Given the significant toxicity with estramustine, its use cannot be encouraged.³

Sipuleucel-T. The use of sipuleucel-T immunotherapy is not recommended in symptomatic disease that necessitates narcotic use, consistent with the FDA indication for this compound.¹⁹

Index Patient 4**10. Clinicians may offer treatment with abiraterone+prednisone to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy. (Option; Evidence Level Grade C)**

In the previously discussed COU-AA-302 study, OS did not meet the pre-specified boundary for significance at the early point of unblinding.¹⁸ Thus, though survival trend is better with abiraterone+prednisone, it remains unclear if abiraterone+prednisone improves OS. Nevertheless, the FDA approved the label for use of abiraterone+prednisone in mCRPC independent of docetaxel treatment. Notably, COU-AA-302 was administered only in good performance status patients, but it is the Panel's opinion that abiraterone+prednisone would be a reasonable alternative to chemotherapy for patients even with a poor performance status.

11. Clinicians may offer treatment with ketoconazole+steroid or radionuclide therapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy who are unable or unwilling to receive abiraterone+prednisone. (Option; Evidence Level Grade C)

Ketoconazole. Ketoconazole has been demonstrated to have anti-cancer effects²⁰ in the setting of mCRPC and could be a viable alternative, in particular if abiraterone+prednisone is unavailable.

Radionuclide therapy. Samarium-153 and strontium-89 have not shown a survival benefit but may offer palliative benefit in patients symptomatic with bone pain.

12. Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy in select cases, specifically when the performance status is directly related to the cancer. (Expert Opinion)

Patients with mCRPC may have a poor performance status for multiple reasons, but the two major possibilities are cancer related and non-prostate cancer related causes. The latter patient may benefit from treatment.

Docetaxel. Docetaxel is considered the standard first-line therapy in mCRPC and has demonstrated both a survival benefit as well as a palliative benefit in symptomatic disease. Most patients with a poor performance status are not considered qualified candidates for chemotherapy, but it is possible that some patients whose cancers are mostly contributing to their disability may benefit from anti-cancer treatment.

Mitoxantrone. Mitoxantrone was approved based on two randomized trials that demonstrated a palliative benefit in symptomatic mCRPC.^{21,24} No survival benefit has been seen with mitoxantrone. However, it could be considered as an alternative option to docetaxel or potentially as a second-line therapy in men with symptomatic disease and a poor performance status. If the poor performance status is not related to cancer progression, then systemic chemotherapy of any kind is not recommended.

13. Clinicians should not offer sipuleucel-T to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

In subsequent analyses of the IMPACT trial, it appears that the survival benefit associated with its use does not appear until six months after therapy.¹⁹ Sipuleucel-T appears to benefit patients with a lower disease burden and better performance status. Patients with very symptomatic disease and a poor performance status would be unlikely to gain a significant survival benefit from the use of sipuleucel-T and should be directed toward alternative options.

Index Patient 5**14. Clinicians should offer treatment with abiraterone+prednisone, cabazitaxel or enzalutamide to patients with mCRPC with good performance status who have received prior docetaxel chemotherapy. If the patient received abiraterone+prednisone prior to docetaxel chemotherapy, he should be offered cabazitaxel or enzalutamide. [Standard; Evidence Level Grade A (abiraterone)/B (cabazitaxel)/A (enzalutamide)]**

Abiraterone+prednisone and enzalutamide have clinical benefit and may be administered with significantly less acute toxicity and no apparent cumulative toxicity as compared to approved chemotherapy in this clinical scenario. This is in contradistinction to cabazitaxel that may show cumulative bone marrow toxicity (manifested by pancytopenia), but also cumulative neurotoxicity, particularly in patients with some underlying peripheral neuropathy from their prior docetaxel.

Abiraterone+prednisone. In a phase III trial (COU-AA-301), patients who had failed docetaxel received abiraterone+prednisone or placebo. At a median of 12.8 months, OS and PFS favored the abiraterone+prednisone cohort.²⁵ As previously noted, abiraterone+prednisone was well tolerated during clinical trial but did show an increase in adverse events, specifically those side effects related to mineralocorticoid excess.

Cabazitaxel. Cabazitaxel is a tubulin-binding taxane chosen for clinical development because of pre-clinical activity in tumor models resistant to other taxanes. An open-label, randomized phase III trial compared cabazitaxel with oral prednisone vs mitoxantrone with the same dose of prednisone, both administered on an every three week basis.²⁶ In this trial, patients who had received prior docetaxel were randomized, and the group receiving cabazitaxel demonstrated improved OS and PFS. Cabazitaxel resulted in more clinically significant diarrhea, but its primary toxicity is hematological, with 82% of patients developing grade 3 or 4 neutropenia, 8% developing febrile neutropenia and 5% deaths. The FDA label indication for this drug recommends prophylactic neutrophil growth factor support in those patients most susceptible to neutropenia, including older individuals and those with significant prior radiotherapy. Because of the need for intravenous administration, the more modest clinical benefit and the higher rates of significant toxicity, cabazitaxel is ranked below abiraterone+prednisone and enzalutamide for this group of patients.

Enzalutamide. Enzalutamide is a novel androgen-receptor signaling inhibitor. The double-blind, placebo controlled phase III AFFIRM trial was performed in men who had received prior docetaxel therapy.²⁷ Patients received either enzalutamide or placebo, and OS, the primary end point, favored enzalutamide. Toxicity from enzalutamide was related primarily to fatigue, diarrhea and hot flashes, although 5 of 800 patients receiving the drug developed seizure activity. This drug was approved by the FDA and represents another highly active oral agent with minimal toxicity available to these patients.

15. Clinicians may offer ketoconazole+steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone+prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)

A number of clinical trials have established the efficacy and toxicity of high-dose ketoconazole in this setting,²⁸ with as many as 50% of patients showing greater than 50% drop in PSA, fewer bidimensionally measurable disease responses and a median time to progression of five to eight months. One study has suggested that 1) prior response to an anti-androgen; 2) pretreatment PSA doubling time; and 3) extent of disease may be associated with the likelihood of clinical response to this therapy.²⁸ Although ketoconazole likely has a lower response rate, a shorter time to progression and higher incidence of significant toxicity than abiraterone+prednisone, it re-

mains a viable alternative for patients unable to obtain abiraterone+prednisone.

16. Clinicians may offer re-treatment with docetaxel to patients with mCRPC with good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy. (Option; Evidence Level Grade C)

In an effort to prolong the overall period of disease control with docetaxel, to allow reversible side-effects to improve and to maximize QOL by spending as much time off chemotherapy as possible, the use of intermittent therapy with built-in drug holidays has become a common practice. Non-randomized data as well as one randomized trial²⁹ suggest that a minority of patients may retain sensitivity to the drug with multiple discontinuous periods of administration. It is apparent that those drug holidays may last, on average, four to five months, and subsequent non-treatment periods might also last a number of months. Patients with these characteristics and who have recovered from prior toxicity may be considered for a re-trial of docetaxel.

Index Patient 6

17. Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone+prednisone, enzalutamide, ketoconazole+steroid or radionuclide therapy. (Expert Opinion)

The goal of palliation is to prevent and relieve suffering and to support the best possible QOL for the patient and family. Advanced prostate cancer can be debilitating with bone pain, fatigue and weight loss. Palliative radiotherapy can be an option for controlling bone pain in some patients.

18. Clinicians should not offer systemic chemotherapy or immunotherapy to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. (Expert Opinion)

There is insufficient evidence demonstrating a benefit in this patient population. The potential for harm greatly outweighs the potential benefit, so these treatments should not be offered.

GUIDELINE STATEMENTS ON BONE HEALTH

Several factors conspire to place the average patient with metastatic prostate at a higher risk of bone complications. First, the median age of onset of the disease is in the late 60's, meaning that the average patient with metastatic disease may be in his 70's (or beyond), clearly a population at risk of physio-

logical, age-related decreases in bone mineral density. Secondly, ADT, a primary therapeutic intervention in patients with recurrent disease, is associated with progressive loss of bone mineral density, not infrequently to the point of measurable osteopenia or frank osteoporosis, increasing the patient's fracture risk even in patients with non-metastatic disease.^{30,31} Finally, in patients with advanced disease, bones are the most common site of metastatic disease with as many as 70% of patients at some point in their course demonstrating evidence of disease in this site.

19. Clinicians should offer preventative treatment (e.g. supplemental calcium, vitamin D) for fractures and skeletal related events to CRPC patients. (Recommendation; Evidence Level Grade C)

Vitamin D

A meta-analysis of randomized controlled trials in over 9,000 patients 60 years of age or older has reported a reduction in the relative risk of hip fracture of 26% (compared to calcium alone or placebo) and of non-vertebral fractures by 23%, although these reductions were only observed with higher doses of vitamin D (700–800 IU/day).³² There was no benefit observed at 400 IU/day, a dose commonly incorporated into multivitamin preparations.

Calcium

Supplemental calcium is recommended in general to help prevent bone loss. This is particularly important in men on either zoledronic acid or denosumab since hypocalcemia requiring dose modification or abandonment is a not-uncommon side effect. However, its use should be tempered by the fact that calcium supplementation alone (500–1,000 mg/day) cannot prevent bone mineral density loss from ADT.³³ Also, calcium supplementation may not be innocuous, as epidemiologic studies have suggested a relationship between calcium intake and the risk of subsequent cardiovascular disease^{34,35} and prostate cancer risk including fatal prostate cancer, though conflicting data exist.^{36,37}

20. Clinicians may choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal related events for mCRPC patients with bony metastases. (Option; Evidence Level Grade C)

Denosumab

Denosumab is a human monoclonal antibody directed against RANKL and inhibits osteoclast-mediated bone destruction. In a randomized trial, patients with mCRPC treated with denosumab demonstrated a longer time to first skeletal-related event compared to zoledronic acid.³⁸ Denosumab resulted in more significant hypocalcemia. For this

reason, when prescribing denosumab, it is recommended to include supplemental calcium and monitor serum calcium level. Osteonecrosis of the jaw was uncommon in both arms. Based on these data, both denosumab and zoledronic acid can be considered options, with denosumab providing slightly superior efficacy results in a head-to-head comparison, and, therefore, is listed as the first option.

Zoledronic Acid

Bisphosphonates are a class of potent inhibitors of bone resorption and have decreased the incidence of SREs. Zoledronic acid is the only bisphosphonate to demonstrate a beneficial effect in patients with mCRPC. In a phase III randomized trial,³⁹ zoledronic acid decreased the incidence of SREs as compared to placebo. Furthermore, longer therapy (up to 24 months) appears to confer continued benefit, even in patients who have experienced one SRE, when compared to placebo. The toxicity of this therapy includes a small incidence of osteonecrosis of the jaw, hypocalcemia and nephrotoxicity.

Radionuclide Therapy

Intravenous radionuclides have been developed in an attempt to palliate patients with painful bony metastases. Samarium-153 has been shown in two randomized trials to provide palliation to patients with painful bony metastases and to have less severe and more transient hematological toxicity, likely related to its shorter half-life^{40,41} that also results in the possibility of giving multiple doses to patients safely.⁴² The toxicity profile alone would result in the selection of samarium-153 over strontium-89 in this group of patients.

Conflict of Interest Disclosures

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received. **Consultant/Advisor: Michael S. Cookson**, Spectrum (C), Myriad (C), US HIFU(C), Endo (C), GE Healthcare (C), Covidien (C); **Stephen J. Freedland**, Amgen (C), Medivation (C), Bayer (C), Mitomics (C), Astellas (C), AstraZeneca (C), Dendreon (C), Janssen (C), Glaxo Smith Kline (C) (Expired); **Maha Hussain**, Merck (C), Lilly (C), Exelixis (C), Johnson & Johnson (C); **Adam S. Kibel**, Dendreon (C), Myriad Genetics (C), National Cancer Institute (C), Sanofi-Aventis (C), Specrum (C); **Daniel W. Lin**, Caris Life Sciences (U), Dendreon Corporation (C), GenProbe (U), Myriad Genetics (C), Pfizer (C); **William T. Lowrance**, Myriad Genetics (C), Dendreon (C); **William K. Oh**, Active Biotech (C), Amgen (C), Astellas (C), Bayer (C), Bellicum Pharmaceuticals (C),

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Guidelines Disclaimer

This document was written by the Castration-Resistant Prostate Cancer Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2011. The Practice Guidelines Committee of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists, and oncologists and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of Castration-Resistant Prostate Cancer. Funding of the committee was provided by the AUA. Committee members received no remuneration for their work. Each member of the

committee provides an ongoing conflict of interest disclosure to the AUA. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ("off label") that are not approved by the Food and Drug Administration, or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

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EXHIBIT H

01 - SOLICITATION DOCUMENT

**THIS DOCUMENT CONTAINS CLAUSES,
PROVISIONS, AND INSTRUCTIONS PERTINENT
TO THIS SOLICITATION.**

READ THIS DOCUMENT IN ITS ENTIRETY.

**DO NOT RETURN THIS DOCUMENT
WITH YOUR OFFER.**

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NOTICE CONCERNING SOLICITATION

DEPARTMENT OF VETERANS AFFAIRS
NATIONAL ACQUISITION CENTER (003B6B)
P.O. BOX 76, Bldg. 37
1st Avenue, 1 Block North of Cermak
HINES, IL 60141

DUE DATE: None
(open and continuous)

CP-FSS-1-C (MAY 2000)

Standing Solicitation No. M5-Q50A-03-R8
(Refreshed 06/21/2018)

WORLDWIDE FEDERAL SUPPLY SCHEDULE CONTRACT
FOR

FSC GROUP 65, PART I, SECTION B

COMMODITY: DRUGS, PHARMACEUTICALS & HEMATOLOGY RELATED PRODUCTS

FSC CLASS(ES) PRODUCT CODE(S):

6505 – DRUGS AND BIOLOGICALS

6508 – MEDICATED COSMETICS AND TOILETRIES

ANY INFORMATION THAT MAY BE DESIRED ON THIS PARTICULAR SOLICITATION CAN BE OBTAINED
FROM THE ISSUING OFFICE ADDRESS SHOWN HEREIN.

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READ ME FIRST**DOING BUSINESS WITH VA**

The Department of Veterans Affairs operates a nationwide system of hospitals, clinics, [Veterans Integrated Service Networks \(VISN\)](#), data processing centers, and National Cemeteries, all of which require a broad spectrum of goods and services. These goods and services are purchased on a national, regional, and local level – so no matter how large or small your business, VA is a potential customer. The [VA Federal Supply Schedule \(FSS\) Program](#) establishes long-term governmentwide contracts that allow *VA and other government agencies* to acquire a vast array of medical equipment and supplies directly from commercial suppliers.

IS A VA FSS CONTRACT RIGHT FOR YOU?

VA awards contracts to responsible companies offering commercial items at fair and reasonable prices. Contracting Officers determine whether prices are fair and reasonable by comparing the prices/discounts that a company offers the government with the prices/discounts offered to commercial customers; this practice is commonly known as “most favored customer” pricing. In order to make this comparison, VA requires offerors to furnish commercial pricelists and disclose information regarding their commercial pricing/discounting practices.

DO YOU QUALIFY FOR A VA FSS CONTRACT?

To qualify for a VA FSS contract you should:

1. Be able to demonstrate that your firm is responsible.
2. Complete the [GSA “Pathway to Success”](#) education seminar. Submit a copy of the certificate of completion with your proposal. Please note that this is only required for new offerors without an existing FSS contract.
3. Meet all the requirements of the solicitation.
4. Be able to fulfill all contract obligations outlined in the solicitation.

Contact the [VA FSS Help Desk](#) to discuss your firm’s eligibility!

IMPORTANT CRITERIA TO CONSIDER

Assess Your Competition

It is recommended that you identify and assess your competition prior to submitting a proposal. This task can be completed by reviewing the [Contract Catalog Search Tool](#), [GSA eLibrary](#) or [GSA Advantage](#). These websites contain information regarding the supplies and services that current VA FSS contractors already offer. Your review of the competition should include: competitor’s pricing, delivery times, warranty terms, services, and any other elements that make their offering distinct when compared to your own.

Best Value Determination

Schedule buyers award task/delivery orders to FSS contractors based upon a “best value” determination. In FAR 2.101, best value is defined as the “expected outcome of an acquisition that, in the Government’s estimation, provides the greatest overall benefit in response to the requirement.” Factors that may be considered when making a best value determination include (but are not limited to):

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- Price
- Special features of the service or supply required for effective performance
- Past performance records
- Quality of the proposed solutions and cost differences
- Trade-in considerations
- Warranty
- Delivery terms
- Expertise of the offeror
- Socioeconomic status

Minimum Sales Criteria

VA expects all FSS contractors to exceed \$25,000 in sales within the first two years after contract award and \$25,000 each succeeding year in order to retain your VA FSS contract. You should consider the difficulty you may have in meeting this performance requirement if your company is newly established or has low sales of the services/supplies you want to offer to the Government. If you decide to submit an offer under the VA FSS program, it is suggested that you draft a business plan covering how you intend to meet this performance requirement.

GETTING ON SCHEDULE

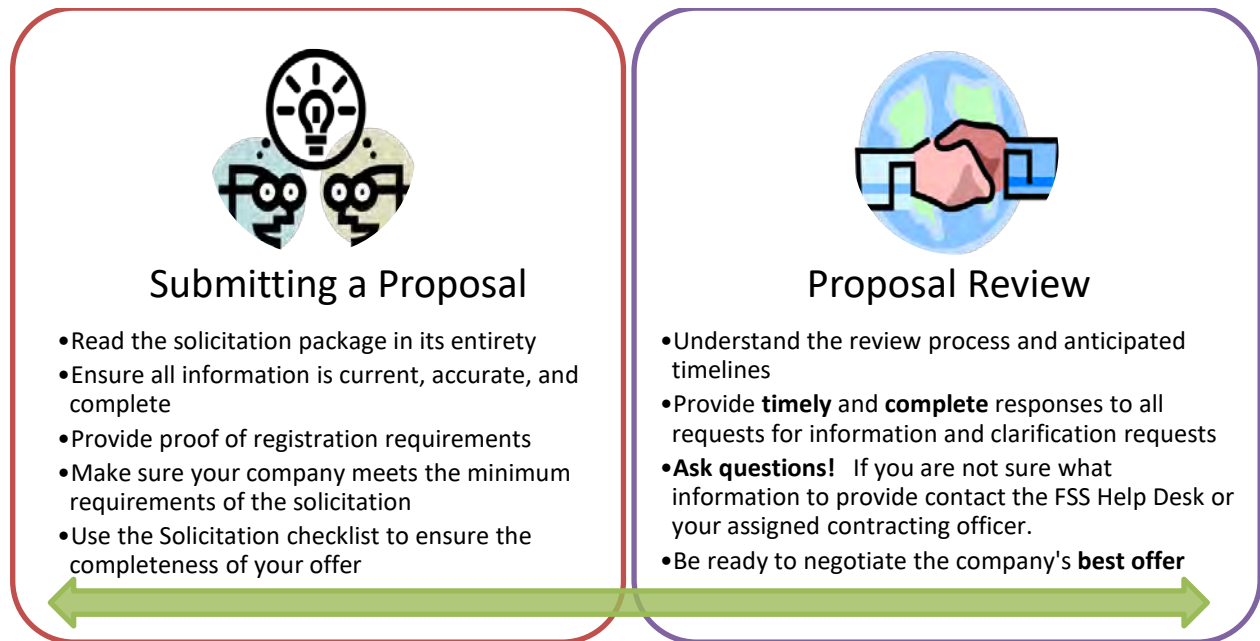
Once you've determined that a VA FSS contract is in your company's best interest you will need to submit an offer for contract award. While not all firms are awarded VA FSS contracts, the VA FSS program is open to all responsible offerors. *To be considered for contract award, you must demonstrate that your firm is responsible and is able to meet all Schedule program requirements, including price reasonableness.* By following the best practices and understanding the review and award processes discussed in this document, vendors will be well equipped to submit a quality offer and negotiate to receive a Schedule contract.

Prior to submitting a proposal, interested companies should:

1. Choose the [Schedule program](#) that best aligns to the supplies and/or services your company wants to offer. Select the appropriate solicitation number to be linked directly to the solicitation files. Download the solicitation, including all corresponding documents, and follow the instructions for completion.
2. Read the entire Schedule solicitation thoroughly and respond to all requirements.
3. Make sure all offered line items fall within the scope of the Schedule solicitation.
4. Make sure the company is financially sound.
5. Be ready to negotiate the company's best offer.

Other helpful hints:

- (1) Obtain a [Data Universal Numbering System \(DUNS\) Number](#), also known as the unique entity identifier.
- (2) Register in the [System for Acquisition Management \(SAM\)](#) database. Vendors **must** be registered in SAM prior to the award of the Schedule contract (see [FAR 52.212-4\(t\)](#)). Contractors that complete electronic annual representations and certifications via the SAM website must update as necessary, but at least annually, to ensure they are kept current, accurate, and complete.
- (3) Submit all required documents including [Manufacturer Letter of Supply](#) and [proof of insurance](#) as required.

BEST PRACTICES**Key Elements of a Successful Offer:**

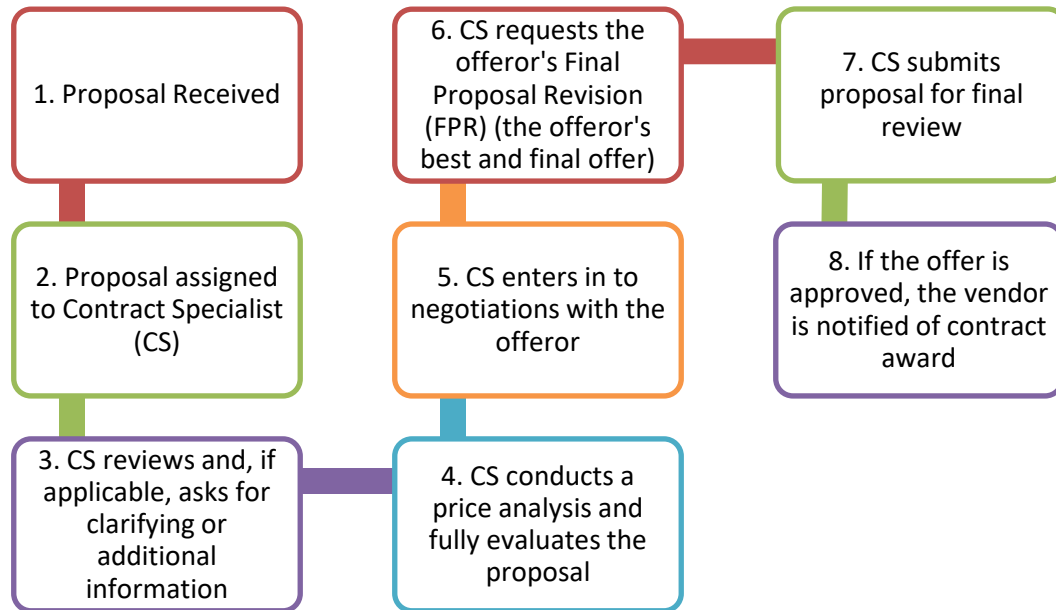
Ensuring these key elements are included in your proposal may expedite the review and award process:

- **Scope** – Are the supplies/services within the scope of the Schedule? See the Scope of Solicitation section in the Vendor Response Document 02.
- **Past Performance** – Does your firm meet its commitments and responsibilities?
- **Financial Capability** – Is your firm financially sound?
- **Pricing** – Is your proposed pricing competitive with current market conditions?
- **Subcontracting Plan** – Required if your firm is considered “other than a small business” and if the estimated value of the contract exceeds \$700,000 (including all option periods).
- **Other Regulatory Compliance** – Is your firm debarred? Are all registration requirements complete? See the [Compliance Requirements](#) web page for a complete list of all required registrations.

Your regional [Procurement Technical Assistance Center \(PTAC\)](#) offers a wide range of assistance (*most free of charge*) through one-on-one counseling, classes, seminars, and matchmaking events. Contact your local PTAC for help in

- Determining your firm’s suitability for contracting
- Proposal preparation
- Securing necessary registrations and socioeconomic registrations
- Researching procurement histories
- Networking
- Identifying bid opportunities
- Contract performance issues
- Preparing for audit

PROPOSAL REVIEW & AWARD PROCESS

Review & Award Process

The goal of this review process is to ensure the vendor is responsible, the Government is receiving a fair and reasonable price, and that any potential contract award is in the best interest of the Government.

Process Time

In general, proposals will be reviewed and, if applicable, awarded **within six (6) months** from the time they are assigned to a Contract Specialist. To further discuss the review process, please contact your assigned contract specialist or the FSS Help Desk. Well prepared offers with competitive pricing are easier to evaluate and, therefore, may expedite the award process. The offer process time can vary depending on:

- The timeliness of your responses to requests for clarification or additional information
- The quality and completeness of the proposal and subsequent clarification responses
- Complexity of the proposal, including number of line items offered
- Quality assurance reviews

TRAINING

Required Training

New offerors without an existing FSS contract must successfully complete GSA's [Pathway to Success](#) at GSA's Vendor Education Center and include a copy of the certificate with their proposal. This seminar is designed to assist prospective Schedule contractors in making an informed business decision as to whether obtaining a GSA Schedule contract is in their best interests.

Please note that the individual whose name appears on the course completion certificate must be an officer of the company and also be designated as an authorized negotiator. This designation is made at K-FSS-1 Authorized Negotiators, located in the Vendor Response section of Document 02. The course must be completed within one year of the date of your proposal (the date listed on the SF 1449).

Recommended Training

The VA FSS Service offers extensive training presentations on our [VA FSS Training](#) web page. Under our “Webinars” section, you will find presentations outlining the steps involved in getting a VA Schedule contract. These presentations describe:

- How to submit an offer
- How to effectively negotiate your offer
- The post-award contract administration process and reporting requirements
- FSS electronic tools

Please utilize the two solicitation guides found in the “Solicitation Assistance” section of our [VA FSS Training page](#). These guides will provide step-by-step instructions for completing the Vendor Response and Commercial Sales Practices sections of the solicitation and will assist you with submitting a more accurately prepared proposal.

Additionally, the [FSS Training](#) page offers best practice tip sheets offering information on the various aspects of the VA Schedules program.

GSA offers numerous in-person and virtual training sessions that provide attendees with an in-depth understanding of acquisition vehicles and policies. Visit the [GSA Interact Training](#) page as well as [GSA's YouTube channel](#) and [Schedule podcast](#) offerings! Additional training is offered by the [GSA Vendor Support Center](#).

Additional Information

While VA provides its Government customers with training in “Using VA Schedules,” including information on the benefits of the Schedules Program, VA does not promote the use of any company’s specific Schedule contract. Vendors should be aware that obtaining a VA Schedule contract is **not a guarantee of sales**. Vendors awarded a VA Schedule contract will need to [market](#) their supplies and services to Government customers as they would to commercial customers.

Contact Us

Contact the [FSS Help Desk](#) for additional information on submitting a proposal or on the VA FSS review and award process!

PART I – TERMS AND CONDITIONS APPLICABLE TO GOODS AND SERVICES**CONTINUATION OF SF-1449 BLOCKS 19-21, SCHEDULE OF ITEMS**

See Continuation of SF-1449 Blocks 19-21, Schedule of Items in Document 02 - Vendor Response.

NATIONAL DRUG CODES (JUN 2005)

NOTE: May not be applicable to SINS 42-1, 42-3, 42-5 and 622.

Offeror is required to enter the National Drug Code following each item pursuant to the instructions of the Commercial Sales Practices (CSP) section of this solicitation. If an NDC has not been assigned, then the offeror should so state. The shipping container shall be marked with the NDC, if available.

BAR CODING (MAY 2012)

All pharmaceutical products provided under this contract shall include bar code labeling at the unit-of-use package level. The bar code labeling must be in a linear format that conforms to all GS1-128 (formerly EAN.UCC) or Health Industry Business Communication Council (HIBCC) Health Industry Bar Code (HIBC) supplier labeling standards. The bar code symbology must comply with all GSI or HIBCC parameters including, but not limited to: symbology type or encoded pattern, bar and space dimensions and tolerances, and allowable ratio of wide to narrow elements.

The bar code may be any linear bar code symbology such as GS1-128 (formerly EAN.UCC), GS1 DataBar (formerly RSS), or Universal Product Code (if the UPC contains the National Drug Code or NDC). The bar code must encode the NDC, either alone or within the GS1 data structure (Global Trade Item Number (GTIN)).

The bar code printing must be American National Standards Institute (ANSI)/International Organization for Standardization (ISO)/IEC Quality Grade C or better. Manufacturers and packagers must ensure that production runs include an initial verification check, as well as routine audits to ensure the bar code is printed clearly and consistently to meet the quality standard of Grade C or better. Contractors shall be responsible for ensuring that bar code labels meet the quality requirements specified in this clause prior to shipping pharmaceutical products to any Government Prime Vendor or authorized ordering activity under this contract.

The bar code must be on the outside container or wrapper of the medication as well as on the immediate container, unless the bar code is readily visible **and** machine-readable through the outside container or wrapper. When the bar code is not easily machine-readable through the over wrap, the over wrap should contain the bar code.

The bar code must go on each cell of a blister pack. Furthermore, the bar code must remain intact under normal conditions of use; thus it should not be printed across the perforations of a blister pack.

When applicable to the symbology used, bar codes shall be surrounded by sufficient quiet zone so that the bar code can be scanned correctly. Bar code placement shall minimize curvature of the bar code. For example, bar codes should be placed in "ladder orientation" on vials or bottles to minimize curvature of the bar code. Bar code labeling shall not be placed solely on outer packaging.

It is recommended that bar code labeling also include the lot number and expiration date. If two separate distinctive bar codes are used, one for NDC and the other for lot number/expiration date, the lot number and expiration date bar code must not be in close proximity to the NDC barcode or in a format that may be confused with the NDC bar code. When applicable, all Healthcare Distribution Management Association (HDMA) guidelines shall be followed.

THERAPEUTIC EQUIVALENCE (FEB 2007)**NOTE: This requirement applies only to SINs 42-2a and 42-2b.**

Only products that have received under the Federal Food, Drug and Cosmetic Act a therapeutic equivalence code of “A” by the Food and Drug Administration will be considered, unless all drugs in the family group are “B” rated. In that case, no award will be made other than to the innovator unless the non-innovator vendor submits acceptable data demonstrating bioequivalence.

AS1345 RECALLS (MAR 2009)

If a drug recall is initiated for any drug provided under this contract, regardless of whether it is a voluntary recall by the manufacturer or a recall required by the U.S. Food and Drug Administration (FDA); or, if FDA withdraws their approval to manufacture any drug that is included on this contract, the following action shall immediately be taken by the contractor:

Forward two copies of the recall notification along with any pertinent information to:

- 1) Chief, Contracting – Administration Section, Federal Supply Schedule Service (003A4B)
VA National Acquisition Center
P.O Box 76
Hines, IL 60141
Fax number (708) 786-4974
- 2) Deputy Chief Consultant (M/S119D)
VHA Pharmacy Benefits Management Services
1st Ave., 1 Block North of Cermak Rd., Bldg. 37, Rm 139
Hines, IL 60141
Fax number (708) 786-7894
- 3) Manager, Product Recall Office
National Center for Patient Safety
Veterans Health Administration
24 Frank Lloyd Wright Drive, Lobby M
Ann Arbor, MI 48106
VHANCPSRecallsNotification@va.gov
Phone Number: (734) 930-5865
- 4) All Government Prime Vendors that were sent shipments of the affected product(s).
- 5) All FSS ordering activities that were sent shipments of the affected product(s).

AS1346 LABELER CODES (JUN 2005)

(This applies to dealers wishing to participate in VA’s Pharmaceutical Prime Vendor (PPV) program. May not be applicable to SINs 42-1, 42-3, 42-5 and 622.)

Dealers must provide their own labeler code, to be used in the National Drug Code (NDC) number for the offered items. If a dealer does not have a labeler code, it must apply and be approved with the U.S. Food & Drug Administration (FDA) for its own labeler code prior to making an offer under this solicitation.

NEW DRUG APPLICATION (NOV 2005)

By signing this solicitation, the offeror certifies that it has on file (if any of the following are required by FDA for the offered drugs) an FDA approved New Drug Application (NDA), an approved abbreviated NDA (ANDA), or a Biologic License approval, as appropriate for the items offered in response to the solicitation.

AS3023 DIVERSION OF PHARMACEUTICAL PRODUCTS (SEP 2010)

- (1) Pharmaceutical products ordered under Federal Supply Schedule (FSS) contracts are intended solely for the use of authorized ordering activities in carrying out their governmental missions; they are not intended for resale or barter. Any transfer of FSS contract items that does not serve the ordering activity's defined mission, as well as any transfer for the purpose of generating a profit on the difference between FSS prices and commercial prices (such as "AWP"), is an improper diversion of government supplies.
- (2) The Contractor may require an ordering activity that is not listed in the appendices to GSA Adm. Order 4800.2E (and its later revisions) or a pharmaceutical prime vendor ordering on an activity's behalf to demonstrate its eligibility to place FSS orders. The Contractor may also require an authorized ordering activity to disclose the intended use of ordered pharmaceuticals before commencing delivery. The Contractor is not required to fill an FSS order (or that portion of an order) that investigational facts suggest will be diverted into the commercial market or will otherwise be diverted from usage by authorized FSS ordering activities. (An example of such facts might be the tripling of usual ordered quantities by an activity, coupled with its failure to demonstrate a corresponding increase in its institutional size or patient base.) However, the Contractor may not unreasonably delay filling an FSS order, pending its investigation of the intended use of the items ordered. Based on investigational facts that suggest that a pattern of diversion has occurred, a Contractor may elect not to fill indirect orders of an activity through an authorized Government PPV and, instead, to accept only direct orders.
- (3) If the Contractor refuses to fill an FSS order because of an expectation that some or all of the order will be diverted or refuses to continue accepting indirect orders because of a perceived pattern of diversion, Contractor must notify the Schedule contracting officer (CO) of its decision within 48 hours and state the basis for the refusal. The CO may instruct the Contractor to fill an executive-agency-level order and/or resume acceptance of executive agency indirect orders if the CO finds that there is no factual basis for the Contractor's decision. No authorized FSS ordering activity may be suspended from eligibility under the Schedule by any Contractor, except on the written instruction of the Schedule CO issued after: a) full consideration of all evidence of diversion or other improper practices, and b) affording the ordering activity an opportunity to present its position on the claimed abuse of the Schedule. An ordering activity suspended by the Schedule CO may appeal that decision in writing to the VA Deputy Assistant Secretary for Acquisition and Materiel Management, within 30 days of the CO's decision.

PART II – CONTRACT TERMS AND CONDITIONS**52.212-4 CONTRACT TERMS AND CONDITIONS—COMMERCIAL ITEMS (JAN 2017) (TAILORED)**

- (a) *Inspection/Acceptance.* The Contractor shall only tender for acceptance those items that conform to the requirements of this contract. The Ordering Activity reserves the right to inspect or test any supplies or services that have been tendered for acceptance. The Ordering Activity may require repair or replacement of nonconforming supplies or reperformance of nonconforming services at no increase in contract price. If repair/replacement or reperformance will not correct the defects or is not possible, the Ordering Activity may seek an equitable price reduction or adequate consideration for acceptance of nonconforming supplies or services. The Ordering Activity must exercise its post-acceptance rights—
 - (1) Within a reasonable time after the defect was discovered or should have been discovered; and

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- (2) Before any substantial change occurs in the condition of the item, unless the change is due to the defect in the item.
- (b) *Assignment*. The Contractor or its assignee may assign its rights to receive payment due as a result of performance of this contract to a bank, trust company, or other financing institution, including any Federal lending agency in accordance with the Assignment of Claims Act ([31 U.S.C. 3727](#)). However, when a third party makes payment (e.g., use of the Governmentwide commercial purchase card), the Contractor may not assign its rights to receive payment under this contract. **NOTE: Please see 52.232-23 Assignment of Claims located within this document under Part II – Contract Terms and Conditions as well as 552.232-23 Assignment of Claims located in the Regulations Incorporated by Reference section of this document.**
- (c) *Changes*. Changes in the terms and conditions of this contract may be made only by written agreement of the parties.
- (d) *Disputes*. This contract is subject to [41 U.S.C. chapter 71](#), Contract Disputes. Failure of the parties to this contract to reach agreement on any request for equitable adjustment, claim, appeal or action arising under or relating to this contract shall be a dispute to be resolved in accordance with the clause at FAR [52.233-1](#), Disputes, which is incorporated herein by reference. **(Note: This clause is included in full text in this solicitation using Alternate I, Dec 1991).** The Contractor shall proceed diligently with performance of this contract, pending final resolution of any dispute arising under the contract.
- (e) *Definitions*. The clause at FAR [52.202-1](#), Definitions, is incorporated herein by reference.
- (f) *Excusable delays*. The Contractor shall be liable for default unless nonperformance is caused by an occurrence beyond the reasonable control of the Contractor and without its fault or negligence such as, acts of God or the public enemy, acts of the Government in either its sovereign or contractual capacity, fires, floods, epidemics, quarantine restrictions, strikes, unusually severe weather, and delays of common carriers. The Contractor shall notify the Contracting Officer in writing as soon as it is reasonably possible after the commencement of any excusable delay, setting forth the full particulars in connection therewith, shall remedy such occurrence with all reasonable dispatch, and shall promptly give written notice to the Contracting Officer of the cessation of such occurrence.
- (g) *Invoice*.
- (1) The Contractor shall submit an original invoice and three copies (or electronic invoice, if authorized) to the address designated in the contract to receive invoices. An invoice must include—
- (i) Name and address of the Contractor;
 - (ii) Invoice date and number;
 - (iii) Contract number, line item number and, if applicable, the order number;
 - (iv) Description, quantity, unit of measure, unit price and extended price of the items delivered;
 - (v) Shipping number and date of shipment, including the bill of lading number and weight of shipment if shipped on Government bill of lading;
 - (vi) Terms of any discount for prompt payment offered;
 - (vii) Name and address of official to whom payment is to be sent;
 - (viii) Name, title, and phone number of person to notify in event of defective invoice; and
 - (ix) Taxpayer Identification Number (TIN). The Contractor shall include its TIN on the invoice only if required elsewhere in this contract.
 - (x) Electronic funds transfer (EFT) banking information.
 - (A) The Contractor shall include EFT banking information on the invoice only if required elsewhere in this contract.

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- (B) If EFT banking information is not required to be on the invoice, in order for the invoice to be a proper invoice, the Contractor shall have submitted correct EFT banking information in accordance with the applicable solicitation provision, contract clause (*e.g.*, [52.232-33](#), Payment by Electronic Funds Transfer—System for Award Management, or [52.232-34](#), Payment by Electronic Funds Transfer—Other Than System for Award Management), or applicable agency procedures.
- (C) EFT banking information is not required if the Government waived the requirement to pay by EFT.
- (2) Invoices will be handled in accordance with the Prompt Payment Act ([31 U.S.C. 3903](#)) and Office of Management and Budget (OMB) prompt payment regulations at 5 CFR Part 1315.
- (h) *Patent indemnity.* The Contractor shall indemnify the Ordering Activity and its officers, employees and agents against liability, including costs, for actual or alleged direct or contributory infringement of, or inducement to infringe, any United States or foreign patent, trademark or copyright, arising out of the performance of this contract, provided the Contractor is reasonably notified of such claims and proceedings.
- (i) *Payment.*—
- (1) *Items accepted.* Payment shall be made for items accepted by the Ordering Activity that have been delivered to the delivery destinations set forth in this contract.
 - (2) *Prompt payment.* The Government will make payment in accordance with the Prompt Payment Act ([31 U.S.C. 3903](#)) and prompt payment regulations at 5 CFR Part 1315.
 - (3) *Electronic Funds Transfer (EFT).* If the Government makes payment by EFT, see [52.212-5\(b\)](#) for the appropriate EFT clause.
 - (4) *Discount.* In connection with any discount offered for early payment, time shall be computed from the date of the invoice. For the purpose of computing the discount earned, payment shall be considered to have been made on the date which appears on the payment check or the specified payment date if an electronic funds transfer payment is made.
 - (5) *Overpayments.* If the Contractor becomes aware of a duplicate contract financing or invoice payment or that the Ordering Activity has otherwise overpaid on a contract financing or invoice payment, the Contractor shall—
 - (i) Remit the overpayment amount to the payment office cited in the contract along with a description of the overpayment including the—
 - (A) Circumstances of the overpayment (*e.g.*, duplicate payment, erroneous payment, liquidation errors, date(s) of overpayment);
 - (B) Affected contract number and delivery order number, if applicable;
 - (C) Affected line item or subline item, if applicable; and
 - (D) Contractor point of contact.
 - (ii) Provide a copy of the remittance and supporting documentation to the Contracting Officer.
- (6) *Interest.*
- (i) All amounts that become payable by the Contractor to the Government under this contract shall bear simple interest from the date due until paid unless paid within 30 days of becoming due. The interest rate shall be the interest rate established by the Secretary of the Treasury as provided in [41 U.S.C. 7109](#), which is applicable to the period in which the amount becomes due, as provided in (i)(6)(v) of this clause, and then at the rate applicable for each six-month period as fixed by the Secretary until the amount is paid.
 - (ii) The Government may issue a demand for payment to the Contractor upon finding a debt is due under the contract.

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- (iii) *Final decisions.* The Contracting Officer will issue a final decision as required by [33.211](#) if—
 - (A) The Contracting Officer and the Contractor are unable to reach agreement on the existence or amount of a debt within 30 days;
 - (B) The Contractor fails to liquidate a debt previously demanded by the Contracting Officer within the timeline specified in the demand for payment unless the amounts were not repaid because the Contractor has requested an installment payment agreement; or
 - (C) The Contractor requests a deferment of collection on a debt previously demanded by the Contracting Officer (see [32.607-2](#)).
- (iv) If a demand for payment was previously issued for the debt, the demand for payment included in the final decision shall identify the same due date as the original demand for payment.
- (v) Amounts shall be due at the earliest of the following dates:
 - (A) The date fixed under this contract.
 - (B) The date of the first written demand for payment, including any demand for payment resulting from a default termination.
- (vi) The interest charge shall be computed for the actual number of calendar days involved beginning on the due date and ending on—
 - (A) The date on which the designated office receives payment from the Contractor;
 - (B) The date of issuance of a Government check to the Contractor from which an amount otherwise payable has been withheld as a credit against the contract debt; or
 - (C) The date on which an amount withheld and applied to the contract debt would otherwise have become payable to the Contractor.
- (vii) The interest charge made under this clause may be reduced under the procedures prescribed in [32.608-2](#) of the Federal Acquisition Regulation in effect on the date of this contract.
- (j) *Risk of loss.* Unless the contract specifically provides otherwise, risk of loss or damage to the supplies provided under this contract shall remain with the Contractor until, and shall pass to the Ordering Activity upon:
 - (1) Delivery of the supplies to a carrier, if transportation is f.o.b. origin; or
 - (2) Delivery of the supplies to the Ordering Activity at the destination specified in the contract, if transportation is f.o.b. destination.
- (k) *Taxes.* The contract price includes all applicable Federal, State, and local taxes and duties.
- (l) *Termination for the Government's convenience.* The Government reserves the right to terminate this contract, or any part hereof, for its sole convenience. In the event of such termination, the Contractor shall immediately stop all work hereunder and shall immediately cause any and all of its suppliers and subcontractors to cease work. Subject to the terms of this contract, the Contractor shall be paid a percentage of the contract price reflecting the percentage of the work performed prior to the notice of termination, plus reasonable charges the Contractor can demonstrate to the satisfaction of the Government using its standard record keeping system, have resulted from the termination. The Contractor shall not be required to comply with the cost accounting standards or contract cost principles for this purpose. This paragraph does not give the Government any right to audit the Contractor's records. The Contractor shall not be paid for any work performed or costs incurred which reasonably could have been avoided.
- (m) *Termination for cause.* The Government may terminate this contract, or any part hereof, for cause in the event of any default by the Contractor, or if the Contractor fails to comply with any contract terms and conditions, or fails to provide the Government, upon request, with adequate assurances of future performance. In the event of termination for cause, the Government shall not be liable to the Contractor for any amount for supplies or services not accepted, and the Contractor shall be liable to

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the Government for any and all rights and remedies provided by law. If it is determined that the Government improperly terminated this contract for default, such termination shall be deemed a termination for convenience.

- (n) *Title*. Unless specified elsewhere in this contract, title to items furnished under this contract shall pass to the Ordering Activity upon acceptance, regardless of when or where the Ordering Activity takes physical possession.
- (o) *Warranty*. Tailored – See Addendum to 52.212-4.
- (p) *Limitation of liability*. Tailored - See Addendum to 52.212-4
- (q) *Other compliances*. The Contractor shall comply with all applicable Federal, State and local laws, executive orders, rules and regulations applicable to its performance under this contract.
- (r) *Compliance with laws unique to Government contracts*. The Contractor agrees to comply with [31 U.S.C. 1352](#) relating to limitations on the use of appropriated funds to influence certain Federal contracts; [18 U.S.C. 431](#) relating to officials not to benefit; [40 U.S.C. chapter 37](#), Contract Work Hours and Safety Standards; [41 U.S.C. chapter 87](#), Kickbacks; [41 U.S.C. 4712](#) and [10 U.S.C. 2409](#) relating to whistleblower protections; [49 U.S.C. 40118](#), Fly American; and [41 U.S.C. chapter 21](#) relating to procurement integrity.
- (s) *Order of precedence*. Any inconsistencies in this solicitation or contract shall be resolved by giving precedence in the following order:
 - (1) The schedule of supplies/services.
 - (2) The Assignments, Disputes, Payments, Invoice, Other Compliances, Compliance with Laws Unique to Government Contracts, and Unauthorized Obligations paragraphs of this clause;
 - (3) The clause at [52.212-5](#).
 - (4) Addenda to this solicitation or contract, including any license agreements for computer software.
 - (5) Solicitation provisions if this is a solicitation.
 - (6) Other paragraphs of this clause.
 - (7) The [Standard Form 1449](#).
 - (8) Other documents, exhibits, and attachments.
 - (9) The specification.
- (t) *System for Award Management (SAM)*.
 - (1) Unless exempted by an addendum to this contract, the Contractor is responsible during performance and through final payment of any contract for the accuracy and completeness of the data within the SAM database, and for any liability resulting from the Ordering Activity's reliance on inaccurate or incomplete data. To remain registered in the SAM database after the initial registration, the Contractor is required to review and update on an annual basis from the date of initial registration or subsequent updates its information in the SAM database to ensure it is current, accurate and complete. Updating information in the SAM does not alter the terms and conditions of this contract and is not a substitute for a properly executed contractual document.
 - (2) (i) If a Contractor has legally changed its business name, "doing business as" name, or division name (whichever is shown on the contract), or has transferred the assets used in performing the contract, but has not completed the necessary requirements regarding novation and change-of-name agreements in FAR [subpart 42.12](#), the Contractor shall provide the responsible Contracting Officer a minimum of one business day's written notification of its intention to
 - (A) change the name in the SAM database;
 - (B) comply with the requirements of [subpart 42.12](#);
 - and (C) agree in writing to the timeline and procedures specified by the responsible Contracting Officer. The Contractor must provide with the notification sufficient documentation to support the legally changed name.

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- (ii) If the Contractor fails to comply with the requirements of paragraph (t)(2)(i) of this clause, or fails to perform the agreement at paragraph (t)(2)(i)(C) of this clause, and, in the absence of a properly executed novation or change-of-name agreement, the SAM information that shows the Contractor to be other than the Contractor indicated in the contract will be considered to be incorrect information within the meaning of the “Suspension of Payment” paragraph of the electronic funds transfer (EFT) clause of this contract.
- (3) The Contractor shall not change the name or address for EFT payments or manual payments, as appropriate, in the SAM record to reflect an assignee for the purpose of assignment of claims (see [subpart 32.8](#), Assignment of Claims). Assignees shall be separately registered in the SAM database. Information provided to the Contractor’s SAM record that indicates payments, including those made by EFT, to an ultimate recipient other than that Contractor will be considered to be incorrect information within the meaning of the “Suspension of payment” paragraph of the EFT clause of this contract.
- (4) Offerors and Contractors may obtain information on registration and annual confirmation requirements via SAM accessed through <https://www.acquisition.gov>.
- (u) Unauthorized Obligations
 - (1) Except as stated in paragraph (u)(2) of this clause, when any supply or service acquired under this contract is subject to any End User License Agreement (EULA), Terms of Service (TOS), or similar legal instrument or agreement, that includes any clause requiring the Government to indemnify the Contractor or any person or entity for damages, costs, fees, or any other loss or liability that would create an Anti-Deficiency Act violation (31 U.S.C. 1341), the following shall govern:
 - (i) Any such clause is unenforceable against the Government.
 - (ii) Neither the Government nor any Government authorized end user shall be deemed to have agreed to such clause by virtue of it appearing in the EULA, TOS, or similar legal instrument or agreement. If the EULA, TOS, or similar legal instrument or agreement is invoked through an “I agree” click box or other comparable mechanism (e.g., “click-wrap” or “browse-wrap” agreements), execution does not bind the Government or any Government authorized end user to such clause.
 - (iii) Any such clause is deemed to be stricken from the EULA, TOS, or similar legal instrument or agreement.
 - (2) Paragraph (u)(1) of this clause does not apply to indemnification by the Government that is expressly authorized by statute and specifically authorized under applicable agency regulations and procedures.
- (v) Incorporation by reference. The Contractor’s representations and certifications, including those completed electronically via the System for Award Management (SAM), are incorporated by reference into the contract.

CLAUSES FOR ADDENDA 52.212-4

52.212-4 (o) (TAILORED)

Warranty: The Contractor warrants and implies that the items delivered hereunder are merchantable and fit for use for the particular purpose described in this contract. In the event that the terms of the contractor’s standard commercial warranty conflict with the warranty terms contained in this clause, the terms of this clause will govern this contract, unless some other resolution is specified in the award document.

**AS13 EXAMINATION OF RECORDS BY VA (MULTIPLE AWARD SCHEDULE)
(FEB 1998)**

- (a) The Contractor agrees that the Secretary of the Department of Veterans Affairs or any duly authorized representative shall have access to, and the right to examine, any books, documents, papers, computer tapes, and any other directly pertinent records of the Contractor to verify that the pre-award pricing, sales, marketing and other data, related to the supplies or services offered under the contract which formed the basis for award, were accurate, complete and current. This right to initiate an audit exists for two (2) years after each of the following events:
- (1) Contract award, or
 - (2) The date of modification adding this clause to the contract, or
 - (3) The date of modification to the contract which requires new Commercial Sales Practices information, with the right, in this instance only, being limited to information contained in the modification.
- (b) The Contractor agrees that the Secretary of the Department of Veterans Affairs or any duly authorized representative shall have access to, and the right to examine, any books, documents, papers, computer tapes, and any other directly pertinent records of the Contractor related to this contract for overbillings, billing errors, compliance with the Price Reduction clause and compliance with the Industrial Funding Fee clause of this contract. The authority to initiate postaward audits shall expire 3 years after final payment. The basic contract and each option shall be treated as separate contracts for purposes of the review for overbillings, billing errors and price reductions. Further information is contained in 552.215-72 Price Adjustment - Failure to Provide Accurate Information (Aug 1997).

**552.216-70 ECONOMIC PRICE ADJUSTMENT—FSS MULTIPLE AWARD
SCHEDULE CONTRACTS (SEP 1999) (ALTERNATE I - SEP 1999)
(DEVIATION I - APR 2007)**

Note 1: For Special Item Number (SIN) 42-2A, paragraph (b) is no longer controlling for covered drugs listed on the FSS at their federal ceiling prices (FCPs). Any request for an economic price adjustment under SIN 42-2A will be determined in accordance with the MA and PPA entered into between the contractor and the VA pursuant to Public Law 102-585. Contractors with dual SIN 42-2A pricelists may apply paragraph (b) to covered drug items on their OGA pricelists. Please see clause AS212 Generic Item Modifications for additional requirements for price increases and decreases for SIN 42-2b.

Note 2: The tracking customer's price must be disclosed with your request for increases. The awarded tracking customer and the established ratio at the time of award will affect your ability to receive an increase.

Price adjustments include price increases and price decreases. Adjustments will be considered as follows:

- (a) Contractors shall submit price decreases anytime during the contract period in which they occur. Price decreases will be handled in accordance with the provisions of the Price Reduction Clause.
- (b) Contractors may request price increases providing all of the following conditions are met:
 - (1) Increases resulting from a reissue or other modification of the Contractor's commercial catalog/pricelist that was used as the basis for the contract award.
 - (2) Increases are requested before the last 60 days of the contract period.
 - (3) At least 30 days elapse between requested increases.
- (c) The following material shall be submitted with the request for a price increase:
 - (1) A copy of the commercial catalog/pricelist showing the price increase and the effective date for commercial customers.

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Defense Authorization Act for Fiscal Year 1991 (Public Law 101-510; 10 U.S.C. 2302 note)) when both the mentor and the protégé are small. There is no exception to joint venture size affiliation for offers received from teaming arrangements under the Department of Defense Pilot Mentor-Protégé Program; and

- (3) See 13 CFR 121.103(b)(9) regarding the exception to affiliation for offers received from Small Business Teaming Arrangements in the case of a solicitation of offers for a bundled contract with a reserve.
- (b) The Government is soliciting and will consider offers from any responsible source, including responsible small business concerns and offers from Small Business Teaming Arrangements or joint ventures of small business concerns.

52.214-34 SUBMISSION OF OFFERS IN THE ENGLISH LANGUAGE (APR 1991)

Offers submitted in response to this solicitation shall be in the English language. Offers received in other than English shall be rejected.

52.214-35 SUBMISSION OF OFFERS IN U.S. CURRENCY (APR 1991)

Offers submitted in response to this solicitation shall be in terms of U.S. dollars. Offers received in other than U.S. dollars shall be rejected.

52.215-20 REQUIREMENTS FOR CERTIFIED COST OR PRICING DATA OR DATA OTHER THAN CERTIFIED COST OR PRICING DATA (OCT 2010) (ALTERNATE IV—OCT 2010)

- (a) Submission of certified cost or pricing data is not required.
- (b) Provide data described below:
 - (1) An offer prepared and submitted in accordance with the clause at 552.212-70, Preparation of Offer (Multiple Award Schedule);
 - (2) Commercial sales practices. The Offeror shall submit information in the format provided in this solicitation in accordance with the instructions at Figure 515.4-2 of the GSA Acquisition Regulation (48 CFR 515-2); or submit information in the format specified in Document 02 in the Commercial Sales Practice Format section. An Excel spreadsheet is provided in 03-Proposal Price List Preparation.
 - (3) Any additional supporting information requested by the Contracting Officer. The Contracting Officer may require additional supporting information, but only to the extent necessary to determine whether the price(s) offered is fair and reasonable.
 - (4) By submission of an offer in response to this solicitation, the Offeror grants the Contracting Officer or an authorized representative the right to examine, at any time before initial award, books, records, documents, papers, and other directly pertinent records to verify the pricing, sales and other data related to the supplies or services proposed in order to determine the reasonableness of price(s). Access does not extend to offeror's cost or profit information or other data relevant solely to the offeror's determination of the prices to be offered in the catalog or marketplace.

52.216-1 TYPE OF CONTRACT (APR 1984)

The Government contemplates award of fixed price with economic price adjustment, indefinite delivery, indefinite quantity (IDIQ) Multiple Award Schedule contracts resulting from this solicitation.

EXHIBIT I

METHODS AND COMPOSITIONS FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate (*i.e.*, 3β -acetoxy- 17 -(3 -pyridyl) androsta- $5,16$ -diene), in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, and at least one additional therapeutic agent such as an anti-cancer agent or a steroid, *e.g.*, a corticosteroid or, more specifically, a glucocorticoid.

BACKGROUND

[0002] The number of people diagnosed with cancer has significantly increased. Of special interest are individuals diagnosed with androgen-dependent disorders, such as prostate cancer, and estrogen-dependent disorders, such as breast cancer since such diagnoses are increasing in number at an alarming rate.

[0003] Prostate cancer is currently the most common non-skin cancer and the second leading cause of cancer-related death in men after lung cancer. The primary course of treatment for patients diagnosed with organ-confined prostate cancer is usually prostatectomy or radiotherapy. Not only are these treatments highly invasive and have undesirable side effects, such localized treatments are not effective on prostate cancer after it has metastasized. Moreover, a large percent of individuals who receive localized treatments will suffer from recurring cancer.

[0004] Additionally, breast cancer incidence in women has increased from one out of every 20 women in 1960 to one out of every eight women in 2005. Moreover, it is the most common cancer among white and African-American women. Similar to treating prostate cancer, most options for women diagnosed with breast cancer are highly invasive and have significant side-effects. Such treatments include surgery, radiation and chemotherapy.

[0005] Hormone therapy is another treatment option for individuals diagnosed with prostate or breast cancer. Hormone therapy is a form of systemic treatment for prostate or breast cancer wherein hormone ablation agents are used to suppress the production or block

the effects of hormones, such as estrogen and progesterone in the body, which are believed to promote the growth of breast cancer, as well as testosterone and dihydrotestosterone, which are believed to promote the growth of prostate cancer. Moreover, hormone therapy is less invasive than surgery and does not have many of the side effects associated with chemotherapy or radiation. Hormone therapy can also be used by itself or in addition to localized therapy and has shown to be effective in individuals whose cancer has metastasized.

[0006] Even though hormone therapy is less invasive and can be used on more advanced stages of cancer, some individuals administered current hormone therapy treatments may not show a significant response or may not show any response at all to such treatments. Additionally, some patients treated with current hormone therapy treatments may also suffer from relapsing or recurring cancer. Currently, such refractory cancer patients are left with very few treatment options.

[0007] Despite the progress made in the treatment of cancer, there remains a need for more effective ways to treat cancer such as, but not limited to, prostate cancer and breast cancer. Additionally, there is a need for effective anti-cancer treatment options for patients who are not responding to current anti-cancer treatments. Also, there is a need for effective anti-cancer treatment options for patients whose cancer has recurred.

SUMMARY OF THE INVENTION

[0008] Described herein are methods for treating a cancer in which a therapeutically effective amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate (*i.e.* 3β -acetoxy-17-(3-pyridyl)androsta-5,16-diene), is administered to a patient, *e.g.*, a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent or steroid. Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, in certain embodiments, the method is directed to treating a refractory cancer in a patient, in which a therapeutically effective amount of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered to a patient currently receiving an anti-cancer agent.

[0009] For example, in certain embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about

100 mg/kg/day of abiraterone acetate and an amount of about 0.1 mg/m² to about 20 mg/m² of mitoxantrone.

[0010] In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 175 mg/m² of paclitaxel.

[0011] In still other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 100 mg/m² of docetaxel.

[0012] Furthermore, described herein is a method for the treatment of a cancer in a mammal comprising administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate; and an amount of about 0.01 mg to about 200 mg of leuprolide, wherein the leuprolide is administered over a period of about 3 days to about 12 months.

[0013] In other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of goserelin, wherein the goserelin is administered over a period of about 28 days to about 3 months.

[0014] Additionally, in another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of triptorelin, wherein the triptorelin is administered over a period of about 1 month.

[0015] The method for the treatment of a cancer in a mammal can also comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 µg/day to about 500 µg/day of seocalcitol, such as about 100 µg/day of seocalcitol.

[0016] Also, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0017] In yet another embodiment, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100

mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0018] Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone.

[0019] Also described herein are compositions for the treatment of cancer that comprise a combination of a therapeutically effective amount of at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and a therapeutically effective amount of at least one additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including, but not limited to, hydrocortisone, prednisone, or dexamethasone.

[0020] Finally, single unit dosage forms comprising abiraterone acetate and a glucocorticoid, optionally with carriers, diluents or excipients, are contemplated. Also, kits comprising at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and an additional anti cancer agent or steroid are contemplated. For example, the kit may include a vial containing abiraterone acetate and another vial containing a glucocorticoid.

Definitions

[0021] As used herein and unless otherwise defined the word “cancer,” refers to the growth, division or proliferation of abnormal cells in the body. Cancers that can be treated with the methods and the compositions described herein include, but are not limited to, prostate cancer, breast cancer, adrenal cancer, leukemia, lymphoma, myeloma, Waldenström’s macroglobulinemia, monoclonal gammopathy, benign monoclonal gammopathy, heavy chain disease, bone and connective tissue sarcoma, brain tumors, thyroid cancer, pancreatic cancer, pituitary cancer, eye cancer, vaginal cancer, vulvar cancer, cervical cancer, uterine cancer, ovarian cancer, esophageal cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, lung cancer, testicular cancer, penal cancer, oral cancer, skin cancer, kidney cancers, Wilms’ tumor and bladder cancer.

[0022] As used herein, and unless otherwise defined, the terms “treat,” “treating” and “treatment” include the eradication, removal, modification, management or control of a

tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

[0023] As used herein, and unless otherwise defined, the term “patient” means an animal, including but not limited to an animal such as a human, monkey, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig. In one embodiment, the patient is a mammal and in another embodiment the patient is a human. In certain embodiments, the patient can be an adult male or female. In some embodiments, the patient is a male of age about 30 years to about 85 years. In other embodiments, the patient is a female of age about 30 years to about 85 years. In a particular embodiment, the patient has or is susceptible to having (*e.g.*, through genetic or environmental factors) cancer. In a further embodiment, the patient has or is susceptible to having (*e.g.*, through genetic or environmental factors) a tumor. In other embodiments, the patient can be castrated or non-castrated.

[0024] The term “ 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor” as used herein refers to an inhibitor of 17α -hydroxylase/ $C_{17,20}$ -lyase, (which is an enzyme in testosterone synthesis), an analog thereof, derivative thereof, metabolite thereof or pharmaceutically acceptable salt thereof. Also, unless otherwise noted, reference to a particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can include analogs, derivatives, metabolites or pharmaceutically acceptable salts of such particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0025] The term “anti-cancer agent” as used herein refers to any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells. It should be noted that even though throughout this specification and in the claims the phrase “anti-cancer agent” is written as a singular noun, for example; “an anti-cancer agent” or “the anti-cancer agent,” the phrase “anti-cancer agent” should not be interpreted as being limited to the inclusion of a single anti-cancer agent.

[0026] As used herein, and unless otherwise defined, the phrase “therapeutically effective amount” when used in connection with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent means an amount of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.

[0027] As used herein and unless otherwise defined the phrase “refractory cancer,” means cancer that is not responding to an anti-cancer treatment or cancer that is not

responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

[0028] As used herein and unless otherwise defined the phrase “refractory patient,” means a patient who has refractory cancer.

[0029] As used herein and unless otherwise defined the phrase “relapse cancer,” means cancer that was at one time responsive to an anti-cancer treatment but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

[0030] As used herein and unless otherwise defined the phrase “recurring cancer,” means cancer that has returned after a patient has been earlier diagnosed with cancer, under gone treatment or had been previously diagnosed as cancer-free.

[0031] As used herein and unless otherwise defined the term “derivative” refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound. The derivative may retain or improve the pharmacological activity of the compound from which it is derived.

[0032] As used herein and unless otherwise defined the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

[0033] As used herein and unless otherwise defined the phrase “pharmaceutically acceptable salt” refers to any salt of a 17 α -hydroxylase/C_{17,20}-lyase inhibitor which retains the biological effectiveness of the 17 α -hydroxylase/C_{17,20}-lyase inhibitor. Examples of pharmaceutically acceptable salts include, but are not limited to, acetates, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartarates, alkanesulfonates (*e.g.* methane-sulfonate or mesylate), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-

sulfonates, and mandelates. Several of the officially approved salts are listed in Remington: The Science and Practice of Pharmacy, Mack Publ. Co., Easton.

DETAILED DESCRIPTION OF THE INVENTION

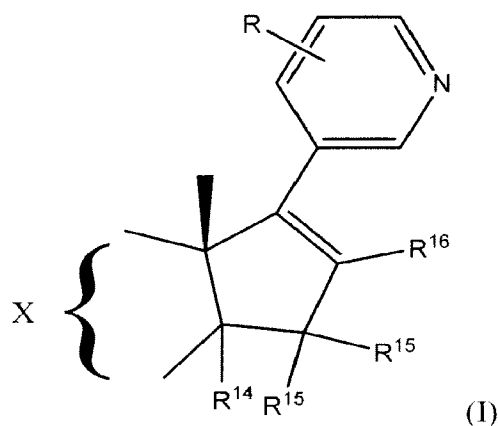
[0034] The methods described herein for treating cancer comprise administering to a mammal, preferably a human, a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor in addition to at least one therapeutic agent, such as an anti-cancer agent or steroid, particularly a glucocorticoid. The compositions described herein comprise a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and at least one additional therapeutic agent, such as an anti-cancer agent or steroid, particularly a corticosteroid or glucocorticoid. Other anti-cancer treatments such as, administration of yet another anti-cancer agent, radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy, can be used with the methods and compositions.

17α -hydroxylase/ $C_{17,20}$ -lyase Inhibitors

[0035] 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors have been shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer respectively, as described in United States Patent No. 5,604,213 to Barrie *et al.*, which is herein incorporated by reference in its entirety.

[0036] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be 17-(3-pyridyl)androsta-5,16-dien-3 β -ol; 17-(3-pyridyl)androsta-3,5,16-triene; 17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol; 17-(3-pyridyl)-5 α -androst-16-en-3 α -ol; 17-(3-pyridyl)-5 α -androst-16-en-3-one; 17-(3-pyridyl)-androsta-4,16-diene-3,11-dione; 17-(3-pyridyl)-androsta-3,5,16-trien-3-ol; 6 α - and 6 β -fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)androsta-4,16-dien-3,6-dione; 3 α -trifluoromethyl-17-(3-pyridyl)androst-16-en-3 β -ol or their acid addition salts and 3-esters as well as metabolites, analogs, derivatives or a pharmaceutically acceptable salt thereof.

[0037] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can have the structure of formula (I):



wherein X represents the residue of the A, B and C rings of a steroid which can be, without limitation, androstan-3 α - or 3 β -ol; androst-5-en-3 α - or 3 β -ol; androst-4-en-3-one; androst-2-ene; androst-4-ene; androst-5-ene; androsta-5,7-dien-3 α or 3 β -ol ; androsta-1,4-dien-3-one; androsta-3,5-diene; androsta-3,5-diene-3-ol; estra-1,3,5[10]-triene; estra-1,3,5[10]-trien-3-ol; 5 α -androstan-3-one; androst-4-ene-3,11-dione; 6-fluoroandrost-4-ene-3-one; or androstan-4-ene-3,6-dione; each of which, where structurally permissible, can be further derivatized in one or more of the following ways, including, but not limited to, to form 3-esters; to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions; as 3-oximes; as 3-methylenes; as 3-carboxylates; as 3-nitriles; as 3-nitros; as 3-desoxy derivatives; to have one or more hydroxy, halo, C₁₋₄ -alkyl, trifluoromethyl, C₁₋₄ -alkoxy, C₁₋₄ -alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring; or to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

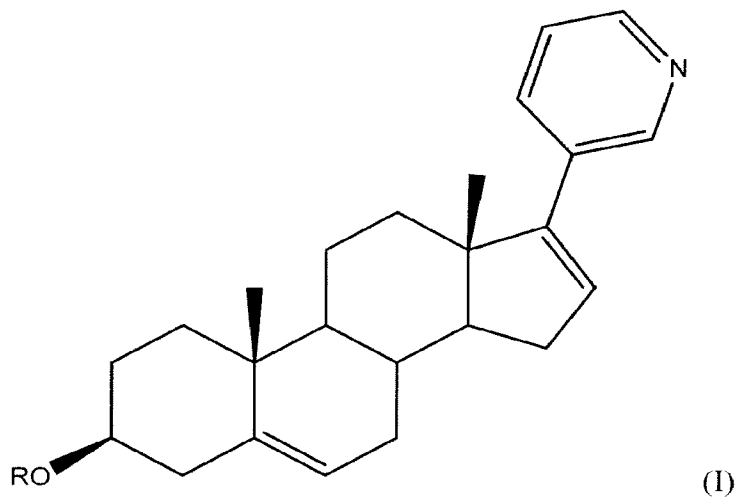
R¹⁴ represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R¹⁵ substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R¹⁴ and one of the R¹⁵ groups together represent a double bond and the other R¹⁵ group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R¹⁶ represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, but excluding 3 β -acetoxy-17-(3-pyridyl)androsta-5,14,16-triene, 3 β ,15 α - and 3 β ,15 β -diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3 β -methoxy-17-(3-pyridyl)-5 α -androst-16-ene.

Suitable inhibitors also include metabolites, derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

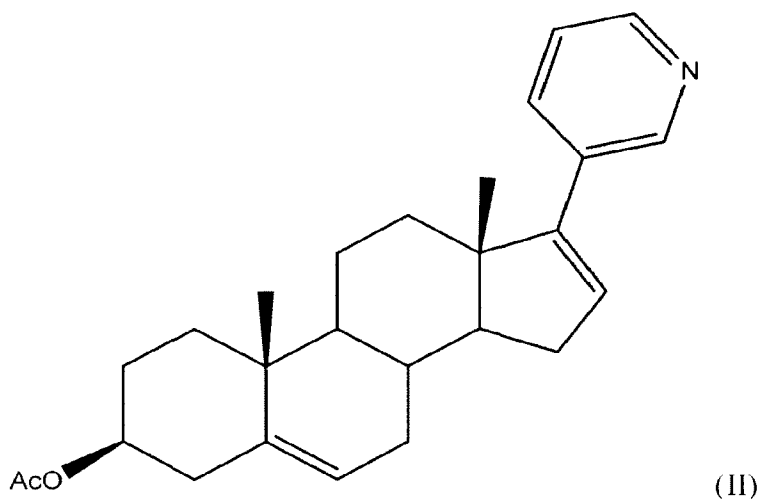
[0038] In another embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can have the structure of formula (I):



wherein R represents hydrogen or a lower acyl group having 1 to 4 carbons. Suitable inhibitors also include derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

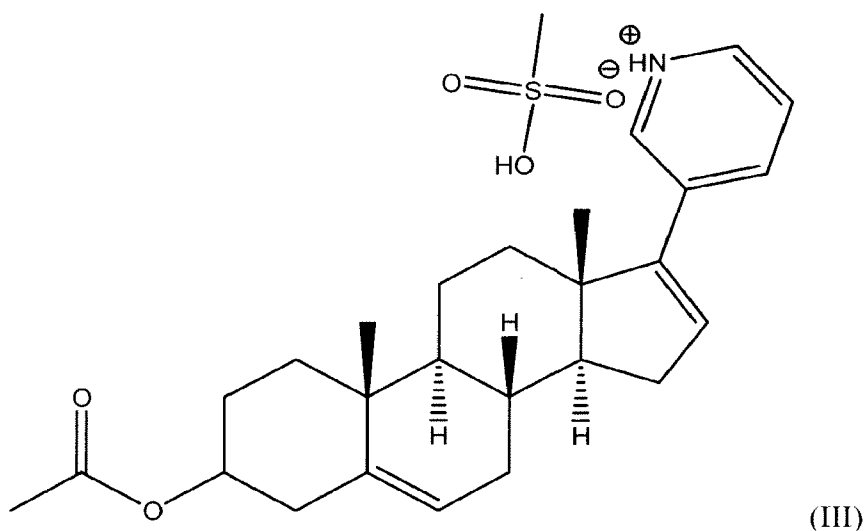
[0039] In still another embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can be a 3 β -alkanoyloxy-17-(3-pyridyl) androsta-5, 16-diene in which the alkanoyloxy group has from 2 to 4 carbon atoms.

[0040] In a preferred embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor comprises abiraterone acetate or 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene which has the following structural formula:



and pharmaceutically acceptable salts thereof.

[0041] Preferred salts of abiraterone acetate and methods of making such salts are also disclosed in United States Provisional Application No. 60/603,559 to Hunt, which is incorporated by reference in its entirety. Preferred salts include, but are not limited to, acetates, citrates, lactates, alkanesulfonates (e.g. methane-sulfonate or mesylate) and tartarates. Of special interest is the abiraterone acetate mesylate salt (*i.e.* 3 β -acetoxy-17-(3-pyridyl)androsta-5,16-diene mesylate salt) which has the following structural formula:



[0042] The 17 α -hydroxylase/C_{17,20}-lyase inhibitors can be made according to any method known to one skilled in the art. For example, such inhibitors can be synthesized according to the method disclosed in United States Patent Nos. 5,604,213 and 5,618,807 to Barrie *et al.*, herein incorporated by reference. Another method of making 17 α -

hydroxylase/C_{17,20}-lyase inhibitors is disclosed in United States provisional application 60/603,558 to Bury, herein incorporated by reference.

[0043] The amount of 17 α -hydroxylase/C_{17,20}-lyase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer, whether the 17 α -hydroxylase/C_{17,20}-lyase inhibitor is administered alone or in combination with an additional anti-cancer treatment, such as an additional anti-cancer agent.

Additional Therapeutic Agents

[0044] Suitable compounds that can be used in addition to 17 α -hydroxylase/C_{17,20}-lyase inhibitors as an anti-cancer agent include, but are not limited to, hormone ablation agents, anti-androgen agents, differentiating agents, anti-neoplastic agents, kinase inhibitors, anti-metabolite agents, alkylating agents, antibiotic agents, immunological agents, interferon-type agents, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, mitotic inhibitors, matrix metalloprotease inhibitors, genetic therapeutics, and anti-androgens. The amount of the additional anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17 α -hydroxylase/C_{17,20}-lyase inhibitor. Below are lists of examples of some of the above classes of anti-cancer agents. The examples are not all inclusive and are for purposes of illustration and not for purposes of limitation. Many of the examples below could be listed in multiple classes of anti-cancer agents and are not restricted in any way to the class in which they are listed in.

[0045] Suitable hormonal ablation agents include, but are not limited to, androgen ablation agents and estrogen ablation agents. In preferred embodiments, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor is administered with a hormonal ablation agent, such as deslorelin, leuprolide, goserelin or triptorelin. Even though throughout this specification and in the claims the phrase “hormonal ablation agent” is written as a singular noun, for example; “a hormonal ablation agent” or “the hormonal ablation agent,” the phrase “hormonal ablation agent” should not be interpreted as being limited to the inclusion of a single hormonal ablation agent. The amount of the hormonal ablation agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17 α -hydroxylase/C_{17,20}-lyase inhibitor.

[0046] Suitable anti-androgen agents include but are not limited to bicalutamide, flutamide and nilutamide. The amount of the anti-androgen agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0047] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with a differentiating agent. Suitable differentiating agents include, but are not limited to, polyamine inhibitors; vitamin D and its analogs, such as, calcitriol, doxercalciferol and seocalcitol; metabolites of vitamin A, such as, ATRA, retinoic acid, retinoids; short-chain fatty acids; phenylbutyrate; and nonsteroidal anti-inflammatory agents. The amount of the differentiating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0048] In another preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-neoplastic agent, including, but not limited to, tubulin interacting agents, topoisomerase inhibitors and agents, acitretin, alstonine, amonafide, amphetinile, amsacrine, ankinomycin, anti-neoplaston, aphidicolin glycinate, asparaginase, baccharin, batracylin, benfluron, benzotript, bromofosfamide, caracemide, carmethizole hydrochloride, chlorsulfaquinoxalone, clanfenur, claviridenone, crisnatol, curaderm, cytarabine, cytosytin, dacarbazine, datelliptinium, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, docetaxel, elliprabin, elliptinium acetate, epothilones, ergotamine, etoposide, etretinate, fenretinide, gallium nitrate, genkwadaphnin, hexadecylphosphocholine, homoharringtonine, hydroxyurea, ilmofofosine, isoglutamine, isotretinoin, leukoregulin, lonidamine, merbarone, merocyanine derivatives, methylanilinoacridine, minactivin, mitonafide, mitoquidone, mitoxantrone, mopidamol, motretinide, N-(retinoyl)amino acids, N-acylated-dehydroalanines, nafazatrom, nocodazole derivative, ocreotide, oquizanocine, paclitaxel, pancratistatin, pazelliptine, piroxantrone, polyhaematoporphyrin, polypreic acid, probimane, procarbazine, proglumide, razoxane, retelliptine, spatol, spirocyclopropane derivatives, spirogermanium, strypoldinone, superoxide dismutase, teniposide, thaliblastine, tocotrienol, topotecan, ukrain, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, and withanolides. The amount of the anti-neoplastic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0049] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be used with a kinase inhibitor including p38 inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics or $\alpha_v\beta_3$ inhibitors. The amount of the kinase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0050] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-metabolite agent. Suitable anti-metabolite agents may be selected from, but not limited to, 5-FU-fibrinogen, acanthifolic acid, aminothiadiazone, brequinar sodium, carmofur, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, doxifluridine, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, isopropyl pyrrolizine, methobenzaprim, methotrexate, norspermidine, pentostatin, piritrexim, plicamycin, thioguanine, tiazofurin, trimetrexate, tyrosine kinase inhibitors, and uricytin. The amount of the anti-metabolite agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0051] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an alkylating agent. Suitable alkylating agents may be selected from, but not limited to, aldo-phosphamide analogues, altretamine, anaxirone, bestrabucil, budotitane, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyplatate, diphenylspiromustine, diplatinum cytostatic, elmustine, estramustine phosphate sodium, fotemustine, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, oxaliplatin, prednimustine, ranimustine, semustine, spiromustine, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol. The amount of the alkylating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0052] In another preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an antibiotic agent. Suitable antibiotic agents may be selected from, but not limited to, aclarubicin, actinomycin D, actinoplanone, adriamycin, aeropylsinin derivative, amrubicin, anthracycline, azino-mycin-A, bisucaberin, bleomycin

sulfate, bryostatin-1, calicheamicin, chromoximycin, dactinomycin, daunorubicin, ditrissarubicin B, dexamethasone, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-Al, esperamicin-Alb, fostriecin, glidobactin, gregatin-A, grincamycin, herbimycin, corticosteroids such as hydrocortisone, idarubicin, illudins, kazusamycin, kesarirhodins, menogaril, mitomycin, neoenactin, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, prednisone, prednisolone, pyridanycin A, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, sorangicin-A, sparsomycin, talisomycin, terpentecin, thiazine, tricrozarin A, and zorubicin. The amount of the antibiotic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0053] Alternatively, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be used with other anti-cancer agents, including but not limited to, acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, amsacrine, anagrelide, anastrozole, anecstim, bexarotene, broxuridine, capecitabine, celmoleukin, cetorelix, cladribine, clotrimazole, daclizumab, dexrazoxane, dilazep, docosanol, doxifluridine, bromocriptine, carmustine, cytarabine, diclofenac, edelfosine, edrecolomab, eflornithine, emitefur, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, glycopine, heptaplatin, ibandronic acid, imiquimod, iobenguane, irinotecan, irsogladine, lanreotide, leflunomide, lenograstim, lentinan sulfate, letrozole, liarozole, lobaplatin, lonidamine, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mitoguazone, mitolactol, molgramostim, nafarelin, nartograstim, nedaplatin, nilutamide, noscapine, oprelvekin, osaterone, oxaliplatin, pamidronic acid, pegaspargase, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, porfimer sodium, raloxifene, raltitrexed, rasburicase, rituximab, romurtide, sargramostim, sizofiran, sobuzoxane, sonermin, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, ubenimex, valrubicin, verteporfin, vinorelbine. The amount of the anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0054] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors may also be administered or combined with steroids, such as corticosteroids or glucocorticoids. The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors and the steroid may be administered in the same or in different compositions. Non-limiting examples of suitable steroids include hydrocortisone, prednisone, or dexamethasone. The amount of the steroid administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0055] In one embodiment, provided herein are methods and compositions comprising both abiraterone acetate and a steroid particularly a corticosteroid, or more particularly a glucocorticoid. Steroids within the scope of the disclosure include, but are not limited to, (1) hydrocortisone (cortisol; cypionate (*e.g.*, CORTEF), oral; sodium phosphate injection (HYDROCORTONE PHOSPHATE); sodium succinate (*e.g.*, A-HYDROCORT, Solu-CORTEF); cortisone acetate oral or injection forms, etc.), (2) dexamethasone (*e.g.*, Decadron, oral; Decadron-LA injection, etc.), (3) prednisolone (*e.g.*, Delta-CORTEF, prednisolone acetate (ECONOPRED), prednisolone sodium phosphate (HYDELTRASOL), prednisolone tebutate (HYDELTRA-TBA, etc.)), or (4) prednisone (*e.g.*, DELTASONE, etc.) and combinations thereof. See, *e.g.*, GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10TH EDITION 2001.

[0056] In a specific embodiment, single unit solid oral dosage forms which comprise an amount from about 50 mg to about 300 mg of abiraterone acetate and an amount from about 0.5 mg to about 3.0 mg of a steroid, *e.g.*, glucocorticoid in a single composition, optionally with excipients, carriers, diluents, etc. is contemplated. For instance, the single unit dosage form can comprise about 250 mg of abiraterone acetate and about 1.0 mg, 1.25 mg, 1.5 mg, or 2.0 mg of a steroid, such as but not limited to corticosteroids or glucocorticoids.

Administration of the 17α -hydroxylase/ $C_{17,20}$ -lyase Inhibitor and an Additional Therapeutic Agent

[0057] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent, such as an anti-cancer agent or a steroid can be administered by any method known to one skilled in the art. In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent can be in separate compositions prior to administration.

In the alternative, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent can be combined into a single composition for administration.

[0058] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the additional therapeutic agent can be administered sequentially or simultaneously. If administered sequentially, the order of administration is flexible. For instance, 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor acetate can be administered prior to administration of the additional therapeutic agent. Alternatively, administration of the additional therapeutic agent can precede administration of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0059] Whether they are administered as separate compositions or in one composition, each composition is preferably pharmaceutically suitable for administration. Moreover, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and the therapeutic agent, if administered separately, can be administered by the same or different modes of administration. Examples of modes of administration include parenteral (*e.g.*, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, intradermal, intraperitoneal, intraportal, intra-arterial, intrathecal, transmucosal, intra-articular, and intrapleural,), transdermal (*e.g.*, topical), epidural, and mucosal (*e.g.*, intranasal) injection or infusion, as well as oral, inhalation, pulmonary, and rectal administration. In specific embodiments, both are oral.

[0060] For example, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered transdermally and the additional therapeutic agent can be administered parenterally. Alternatively, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered orally, such as in a tablet, caplet or capsule, while the additional therapeutic agent can be administered intravenously. Such intravenous administered therapeutic agents include, but are not limited to, docetaxel injections, such as Taxotere[®]; paclitaxel injections, such as Paclitaxel[®] and mitoxantrone injections, such as Novantrone[®]. Also, the additional therapeutic agent can be in the form of depots or implants such as leuprolide depots and implants, *e.g.* Viadur[®] and Lupron Depot[®]; triptorelin depots, *e.g.* Trelstar[®]; goserelin implants, *e.g.* Zoladex[®].

[0061] The suitable daily dosage of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor depends upon a number of factors, including, the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, and response of the individual patient. Suitable daily dosages of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day, or

from about 0.001 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 100 mg/kg/day in single or multiple doses.

[0062] In some embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered in an amount from about 0.004 mg/day to about 5,000 mg/day, or from about 0.04 mg/day to about 3,000 mg/day, or from about 0.4 mg/day to about 1500 mg/day. In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be administered in an amount from about 0.1 mg/day to about 2000 mg/day or from about 1 mg/day to about 2000 mg/day or from about 50 mg/day to about 2000 mg/day or from about 100 mg/day to about 1500 mg/day or from about 5 mg/day to about 1,000 mg/day or from about 5 mg/day to about 900 mg/day or from about 10 mg/day to about 800 mg/day or from about 15 mg/day to about 700 mg/day or from about 20 mg/day to about 600 mg/day or from about 25 mg/day to about 500 mg/day in single or multiple doses.

[0063] In certain embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is co-administered with an additional anti-cancer agent such as mitoxantrone, paclitaxel or docetaxel. For example, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of mitoxantrone. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the mitoxantrone can be administered in an amount of about 0.1 mg/m² to about 20 mg/m². Preferably, the mitoxantrone is administered over a period of between about 10 to about 20 minutes once every 21 days.

[0064] Also, a method for the treatment of a cancer in a mammal can comprise administering an amount of abiraterone acetate and an amount of paclitaxel. In one embodiment, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the paclitaxel can be administered in the amount of about 1 mg/m² to about 175 mg/m². Preferably, the paclitaxel is administered over a period of between about 2 to about 5 hours once every three months.

[0065] Additionally, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of docetaxel. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the docetaxel can be administered in an amount of about 1 mg/m² to about 100 mg/m². Preferably, the docetaxel is administered over a period of between about 1 to about 2 hours once every three weeks.

[0066] In certain embodiments, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor is administered along with an anti-cancer agent that comprises a hormonal ablation agent, including, but not limited to, leuprolide, goserelin, or triptorelin. For example, one method for the treatment of a cancer in a mammal also comprises administering an amount of abiraterone acetate and an amount of leuprolide. The amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of leuprolide can be about 0.01 mg to about 200 mg over a period of about 3 days to about 12 months. Preferably, the leuprolide is administered in the amount of about 3.6 mg of leuprolide over a period of about 3 days to about 12 months.

[0067] Additionally, the methods for the treatment of cancer in a mammal include administering an amount of abiraterone acetate and an amount of goserelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of goserelin can be about 0.01 mg to about 20 mg over a period of about 28 days to about 3 months. Preferably, the goserelin is administered in the amount of about 3.6 mg to about 10.8 mg over a period of about 28 days to about 3 months.

[0068] In certain embodiments the methods for the treatment of cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of triptorelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of triptorelin can be about 0.01 mg to about 20 mg, over a period of about 1 month, preferably the triptorelin is administered in the amount of about 3.75 mg over a period of about 1 month.

[0069] Also, in one embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of seocalcitol. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 μ g/day to about 500 μ g/day of seocalcitol, such as about 100 μ g/day of seocalcitol.

[0070] In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of bicalutamide. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0071] In yet another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of

flutamide. For example, the method comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0072] Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor such as abiraterone acetate and an amount of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of hydrocortisone. In other instances, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of hydrocortisone.

[0073] The method for the treatment of a cancer can also comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as prednisone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of prednisone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of prednisone.

[0074] In addition, the method for the treatment of a cancer can also comprise administering an amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of dexamethasone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 0.5 mg/day to about 25 mg/day of dexamethasone.

Compositions Containing a 17α -hydroxylase/ $C_{17,20}$ -lyase Inhibitor and an Additional Therapeutic Agent

[0075] In certain embodiments, the compositions can contain a combination of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, preferably abiraterone acetate, and any of the therapeutic agents recited above. Whether the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and

the additional therapeutic agent are administered in separate compositions or as a single composition, the compositions can take various forms. For example, the compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders or sustained-release formulations, depending on the intended route of administration.

[0076] For topical or transdermal administration, the compositions can be formulated as solutions, gels, ointments, creams, suspensions or salves.

[0077] For oral administration, the compositions may be formulated as tablets, pills, dragees, troches, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0078] The composition may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas that contain conventional suppository bases such as cocoa butter or other glycerides.

[0079] In addition to the formulations described previously, the composition may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the therapeutic agents may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0080] Additionally, the composition may be delivered using a sustained-release system, such as semi-permeable matrices of solid polymers containing the composition. Various forms of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature can release the composition over a period of hours, days, weeks, months. For example a sustained release capsule can release the compositions over a period of 100 days or longer. Depending on the chemical nature and the biological stability of the composition, additional strategies for stabilization may be employed.

[0081] The compositions can further comprise a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered.

[0082] For parenteral administrations, the composition can comprise one or more of the following carriers: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial

agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0083] For oral solid formulations suitable carriers include fillers such as sugars, *e.g.*, lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, fats and oils; granulating agents; and binding agents such as microcrystalline cellulose, gum tragacanth or gelatin; disintegrating agents, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate, Primogel, or corn starch; lubricants, such as magnesium stearate or Sterotes; glidants, such as colloidal silicon dioxide; a sweetening agent, such as sucrose or saccharin; or flavoring agents, such as peppermint, methyl salicylate, or orange flavoring. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

[0084] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy injectability with a syringe. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars; polyalcohols such as mannitol, sorbitol; sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0085] Also for intravenous administration, the compositions may be formulated in solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In a preferred embodiment, the compositions are formulated in sterile solutions.

[0086] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

[0087] For administration by inhalation, the compositions may be formulated as an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the composition and a suitable powder base such as lactose or starch.

[0088] The pharmaceutical compositions may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

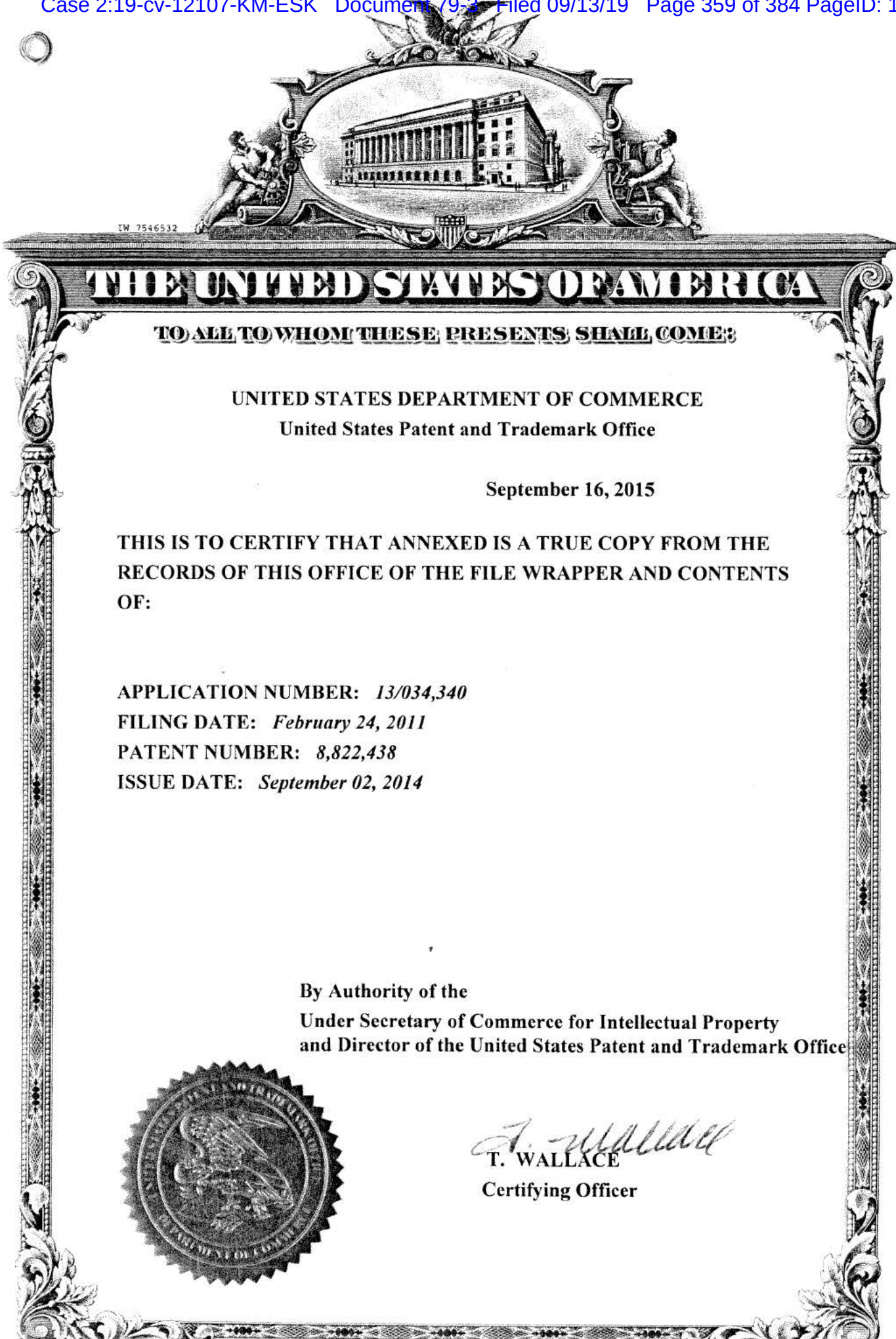
[0089] One example of a composition comprising a 17 α -hydroxylase/C_{17,20}-lyase inhibitor and an additional therapeutic agent is an oral composition or composition suitable for oral administration comprising abiraterone acetate in combination with a steroid. For example, the oral composition can be a solid dosage form such as a pill, a tablet or a capsule. The oral composition can comprise about 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of abiraterone acetate. The oral composition can comprises about 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 7.5 mg, 10 mg, 20 mg, 30 mg, 40 mg or 50 mg of a steroid, such as a glucocorticoid.

[0090] In one embodiment, the oral composition can comprise about 50 mg to about 500 mg of abiraterone acetate and an amount of about 0.25 mg to about 3.5 mg of the

steroid, such as hydrocortisone, prednisone or dexamethasone. In other instances, the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and an amount of about 1.0 mg to about 2.5 mg of the steroid, such as hydrocortisone, prednisone or dexamethasone. In another embodiment the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and about 0.5 mg to about 3.0 mg of a steroid. For example, the oral composition can be a tablet containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients. Additionally, the oral composition can be a capsule containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients.

[0091] The description contained herein is for purposes of illustration and not for purposes of limitation. The methods and compositions described herein can comprise any feature described herein either alone or in combination with any other feature(s) described herein. Changes and modifications may be made to the embodiments of the description. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

EXHIBIT J



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Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office



T. Wallace
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Certifying Officer

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International Application Number:	
Confirmation Number:	1597
Title of Invention:	Methods and Compositions for Treating Cancer
First Named Inventor/Applicant Name:	Alan H. Auerbach
Customer Number:	27777
Filer:	Timothy E. Tracy/Laurie Russo
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Other Reference-Patent/App/Search documents	CGR5001_REFS_FROM_PAIR.pdf	1879808 351692168f177b6ceaa9a9d7e3505fe307d82c42	no	23

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

LIST OF REFERENCES CITED BY APPLICANTS
(Use several sheets if necessary)

Application Number	11/844,440
Filing Date	August 24, 2007
First Named Inventor	Auerbach <i>et al.</i>
Art Unit	1628
Examiner Name	HUI, San Ming R.
Attorney Docket No.	11515-004-999

U.S. PATENT DOCUMENTS

*Examiner Initials	Cite No.	Document Number – Kind Code	Publication Date Mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

*Examiner Initials	Cite No.	Foreign Patent Document Country Code, Number, Kind Code (if known)	Publication Date Mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T

NON PATENT LITERATURE DOCUMENTS

*Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
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Application Number	11/844,440
Filing Date	August 24, 2007
First Named Inventor	Auerbach <i>et al.</i>
Art Unit	1617
Examiner Name	HUI, San Ming R.
Attorney Docket No.	11515-004-999

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	FILING DATE August 24, 2007	ART UNIT 1617

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First Named Inventor	Auerbach <i>et al.</i>
Art Unit	1617
Examiner Name	Hui, San Ming R
Attorney Docket No.	11515-004-999

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